2.04.45	Somatic (Tumor) Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)		
Original Policy Date:	August 31, 2015	**Effective Date:**	February 1, 2023
Section:	2.0 Medicine	**Page:**	Page 1 of 73

Policy Statement

Note: Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

The use of tissue samples for analysis is generally preferred over plasma testing (liquid biopsy or circulating tumor DNA, ctDNA) when available. Panel testing of tissue samples is an acceptable alternative to individual testing when the quantity of tissue is limited. Plasma testing is generally unavailable for single genes or exons and are typically performed as a panel test.

Molecular analysis related to this policy (genetic testing) is reserved for advanced (stage III or IV) or metastatic Non-Small-Cell Lung Cancer (NSCLC) including adenocarcinoma, large cell, squamous cell and NSCLC not otherwise specified (see Policy Guidelines) or if a targeted therapy dependent on genetic testing is being considered. Small panel tissue testing including the following medically necessary genes may be considered as an alternative to individual testing and may be preferred when there is limited tissue available for testing.

Plasma Testing When Tissue is Insufficient

I. Plasma tests for oncogenic driver variants deemed medically necessary on tissue biopsy may be considered **medically necessary** to predict treatment response to targeted therapy for individuals when they do not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue.

II. Follow-up tissue-based analysis may be considered **medically necessary** should no driver variant be identified via plasma testing.

***EGFR* Testing**

III. The epidermal growth factor receptor *(EGFR)* gene, may be considered **medically necessary** initially to predict treatment response to an FDA-approved therapy (e.g., erlotinib [Tarceva®] alone or in combination with ramucirumab [Cyramza®], gefitinib [Iressa®], afatinib [Gilotrif®], dacomitinib [Vizimpro®], or osimertinib [Tagrisso™]). Technically, the analysis of tumor tissue for somatic variants would be in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q).

IV. Analysis of tumor tissue for somatic variants in exon 20 (e.g., insertion mutations) within the *EGFR* gene, may be considered **medically necessary** to predict treatment response to an FDA-approved therapy (e.g., mobocertinib [Exkivity] or amivantamab [Rybrevant]). However, testing is typically just ordered for EGFR analysis (alone or in a panel) rather than for specific exons.

V. At progression (or when included in an initial panel), repeat analysis of either a new tissue sample or plasma of (the EGFR T790M resistance variant) for targeted therapy with osimertinib may be considered **medically necessary** in individuals with advanced or high risk

earlier stage (IB-IIIA) lung adenocarcinoma, large cell carcinoma, advanced squamous-cell non-small-cell lung cancer, and non-small-cell lung cancer not otherwise specified.

Patients with wild-type variants are unlikely to respond to targeted therapy; for these patients, other treatments should be considered.

VI. Analysis of somatic variants in the EGFR gene in tissue or plasma, including variants within exons 22 to 24, is considered **investigational** in all other situations unless included in the general analysis of EGFR.

ALK Testing

VII. Individual analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (*ALK*) gene may be considered **medically necessary** to predict treatment response to an FDA-approved ALK inhibitor therapy (e.g., crizotinib [Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], brigatinib [Alunbrig™], or lorlatinib [Lorbrena®]) or when part of an approved panel.

VIII. Analysis of somatic rearrangement variants of the *ALK* gene in tissue or plasma is considered **investigational** in all other situations.

BRAF V600E Testing

IX. Individual analysis of the somatic *BRAF* V600E variant may be considered **medically necessary** to predict treatment response to an FDA-approved BRAF and/or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]), or when part of an approved panel.

X. Analysis of tumor tissue for the somatic *BRAF* V600E variant is considered **investigational** in all other situations.

ROS1 Testing

XI. Individual analysis for somatic rearrangement variants of the *ROS1* gene may be considered **medically necessary** to predict treatment response to an FDA-approved ROS1 inhibitor therapy (e.g., crizotinib [Xalkori®] or entrectinib [Rozlytrek®]) or when part of an approved panel.

XII. Analysis of somatic rearrangement variants of the *ROS1* gene is considered **investigational** in all other situations.

KRAS Testing

XIII. Individual analysis of somatic variants of the *KRAS* gene (e.g., G12C) may be considered **medically necessary** to predict treatment response to sotorasib (Lumakras) or when part of an approved panel.

XIV. All other uses of analysis of somatic variants of the *KRAS* gene are considered **investigational**.

HER2 Testing

XV. Individual analysis of somatic alterations in the *HER2* (*ERBB2*) gene may be considered **medically necessary** to predict treatment response to an FDA-approved therapy (e.g., fam-trastuzumab deruxtecan-nxki [Enhertu®]) or when part of an approved panel.

XVI. All other uses of analysis of somatic variants of the *HER2* (*ERBB2*) gene are considered **investigational**.

RET Rearrangement Testing

XVII. Individual analysis of somatic alterations in the *RET* gene may be considered **medically necessary** to predict treatment response to pralsetinib (Gavreto) or selpercatinib (Retevmo) or when part of an approved panel.

XVIII. Analysis of tumor tissue for somatic alterations in the *RET* gene is considered **investigational** in all other situations.

MET Exon 14 Skipping Alteration

XIX. Individual analysis of somatic alterations that leads to *MET* exon 14 skipping may be considered **medically necessary** to predict treatment response to capmatinib (Tabrecta) or when part of an approved panel.

XX. All other uses of analysis of somatic variants of the *MET* gene in tissue or plasma are considered **investigational**.

PD-L1 Testing

XXI. Programmed Death-Ligand 1 (PD-L1) testing may be considered **medically necessary** to predict treatment response to an FDA-approved therapy (e.g., atezolizumab [Tecentriq], nivolumab [Opdivo] in combination with ipilimumab [Yervoy], pembrolizumab [Keytruda], or cemiplimab-rwlc [Libtayo]) in individuals with NSCLC or when part of an approved panel.

Note: PD-L1 is a ligand not a gene, and testing may be requested separately if not part of the panel.

XXII. PD-L1 testing is considered **investigational** in all other situations.

Tumor Mutational Burden Testing

XXIII. Analysis of tumor mutational burden to predict treatment response to immunotherapy (e.g., pembrolizumab or Keytruda) in individuals with resistant or progressive cancer that has failed all standard regimens may be considered **medically necessary**.

XXIV. Analysis of tumor mutational burden is considered **investigational** in all other circumstances.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

These gene tests are intended for use in patients with advanced (stage III or IV) non-small-cell lung cancer.

ctDNA tests: The cobas® test is a companion diagnostic for erlotinib (Tarceva®; OSI Pharmaceuticals, Melville NY). Guardant 360 has 2 similar tests, each about 70+ genes. The CDx version is a new FDA approved companion diagnostic for the EGFR exon 19 deletions, L858R and T790M mutation associated with using osimertinib (TAGRISSO®), and it includes SNV testing for NTRK1 and NTRK3 as well as fusion testing for NTRK1 and uses the CPT PLA code 0242U. The Guardant LDT is a laboratory developed test, which tests for all 3 NTRK genes (NTRK1, NTRK2 and NTRK3), also includes MSI (Microsatellite Instability) and Tumor Mutational Burden (TMB) and should use a miscellaneous CPT code of 81455 (sometimes billed as 81479). Either test is acceptable for use with NSCLC. The FoundationOne Liquid CDx is a 300+ gene panel companion diagnostic for multiple treatments including those related to EGFR and includes MSI and TMB. It is billed using CPT code 0239U and has a similar gene panel to their solid tumor test (FoundationOne CDx).

NTRK testing can also be done using IHC (ImmunoHistoChemical, usually Pan-TRK IHC) or FISH testing if not done as part of a gene panel. NTRK fusions represent up to 1/30 NSCLCs (Vaishnavi et al. Nature Medicine 2013).

NTRK (neurotrophic tyrosine receptor kinase) gene fusions happen when a piece of chromosome containing the NTRK gene breaks off and joins (fuses) with a gene on another chromosome, producing abnormal proteins that can cause cancer cells to grow. It has been associated with cancers of brain, head and neck, thyroid, soft tissue, lung, and colon.

This policy does not address NTRK testing.

This policy does not address germline testing for inherited risk of developing cancer.

For expanded panel testing, see Blue Shield of California Medical Policy: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

Tumor Mutational Burden or TMB, is defined as the number of somatic mutations per megabase of a genomic sequence, and varies by type of cancer. Whole exome sequencing-derived TMB was initially common but **large** panel sequencing-based estimates of TMB are increasingly common. TMB has been proposed to predict the efficacy of immune checkpoint inhibitors like pembrolizumab (Keytruda®) for a variety of cancers. A result of greater than 10 is considered to be a high TMB and less than10 is low.

For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms. The most recent guidelines (v.5.2022) recommend that *EGFR* variants (category 1), *ALK* rearrangements (category 1), and PD-L1 testing (category 1) as well as *KRAS*, *ROS1*, *BRAF, NTRK1/2/3, MET* exon 14 skipping alteration*, RET,* and *HER2* testing (all category 2A) be performed in the workup of non-small-cell lung cancer in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified. The guidelines add that testing should be conducted as part of broad molecular profiling, defined as a single assay or a combination of a limited number of assays and that it is acceptable to have a tiered approach based on low-prevalence, co-occurring biomarkers. The guidelines additionally recommend identifying the emerging biomarker, high-level MET amplification, while noting that the definition of this biomarker is evolving and may differ according to the assay used.

The 2018 guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology have recommended the following:

> "One set of genes must be offered by all laboratories that test lung cancers, as an absolute minimum: EGFR, ALK, and ROS1. A second group of genes should be included in any expanded panel that is offered for lung cancer patients: BRAF, MET, RET, ERBB2 (HER2), and KRAS, if adequate material is available. KRAS testing may also be offered as a single-gene test to exclude

patients from expanded panel testing. All other genes are considered investigational at the time of publication."

Repeat Genomic Testing

There may be utility in repeated testing of gene variants for determining targeted therapy or immunotherapy in individuals with NSCLC, as tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making. For example, repeat testing (tissue or liquid based) of EGFR for T790M at progression on or after EGFR tyrosine kinase inhibitor therapy may be considered to select patients for treatment with osimertinib. T790M is an acquired resistance mutation that is rarely seen at initial diagnosis. The American Society of Clinical Oncology (ASCO) currently suggests repeat genomic testing for individuals on targeted therapy with suspected acquired resistance, especially if choice of next-line therapy would be guided. The ASCO guidance is not tumor specific, and it cautions to consider clinical utility (Chakravarty et al, 2022; PMID 35175857).

Concurrent Somatic Liquid-Based and Tissue-Based Genomic Testing

Liquid biopsy testing uses blood samples and assesses cancer DNA and non-cancer DNA in the same blood sample. The goal is to identify options for genome-informed treatment. Some providers will order a liquid biopsy test and a tissue biopsy test at the same time to hasten time to treatment. If the intent of concurrent testing is to follow an individual over time to monitor for resistance variant T790M, then consideration could be given to doing liquid biopsy at diagnosis with the tissue biopsy to make sure that mutations that are going to be followed longitudinally can be detected by the liquid biopsy. Current NCCN guidelines for NSCLC (v. 5.2022) state the following: "Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity, but significantly compromised sensitivity, with up to a 30% false-negative rate; however, data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection."

Recommended Testing Strategies

Patients who meet criteria for genetic testing as outlined in the policy statements above should be tested for the variants specified.

- When tumor tissue is available, use of tissue for testing of any/all variants and biomarkers outlined in this policy is recommended, but is not required in all situations. In certain situations, circulating tumor DNA testing (liquid biopsy) may be an option.

Coding

The following CPT code is specific for testing for common variants of *EGFR*:

- **81235**: *EGFR (epidermal growth factor receptor)* (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)

If testing is done by immunohistochemical assay, the following CPT code would likely be reported:

- **88342**: Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure

If testing is done by fluorescence in situ hybridization, the following CPT code would likely be reported:

- **88365**: In situ hybridization (e.g., FISH), per specimen; initial single probe stain procedure

The following CPT codes are specific for testing for *KRAS*:

- **81275**: KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)

- **81276**: KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)

The following Molecular Pathology codes are to support Neurotrophic receptor tyrosine kinase (NTRK) gene testing:

- **81191:** NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis
- **81192:** NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis
- **81193:** NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis
- **81194:** NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis

The following CPT code has a listing for *RET* testing:

- **81404**: Molecular Pathology Procedure Level 5
  - *RET (ret proto-oncogene)* (e.g., multiple endocrine neoplasia, type 2B and familial medullary thyroid carcinoma), common variants (e.g., M918T, 2647_2648delinsTT, A883F)

The following CPT code has listings for both *KRAS* and *RET* testing:

- **81405**: Molecular Pathology Procedure Level 6
  - *KRAS (Kirsten rat sarcoma viral oncogene homolog)* (e.g., Noonan syndrome), full gene sequence
  - *RET (ret proto-oncogene)* (e.g., multiple endocrine neoplasia, type 2A and familial medullary thyroid carcinoma), targeted sequence analysis (e.g., exons 10, 11, 13-16)

The following CPT code has a listing for *BRAF* testing:

- **81406**: Molecular Pathology Procedure Level 7
  - *BRAF* (B-*Raf proto-oncogene, serine/threonine kinase*) (e.g., Noonan syndrome), full gene sequence

Testing for variants in the other genes listed above would be reported with the following code:

- **81479**: Unlisted molecular pathology procedure

Description

Over half of patients with non-small-cell lung cancer (NSCLC) present with advanced and therefore incurable disease. Treatment in this setting has been with platinum-based chemotherapy. The identification of specific, targetable oncogenic "driver mutations" in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes that may direct targeted therapy or immunotherapy depending on the presence of specific variants.

Related Policies

- Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract

language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Table 1 summarizes the FDA-approved targeted treatments for patients with NSCLC along with the concurrently approved companion diagnostic tests. (Note this information is current as of October 17, 2022. FDA maintains a list of cleared or approved companion diagnostics at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.)

Table 1. FDA-Approved Targeted Treatments for NSCLC and Companion Diagnostic Tests

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
Afatinib (Gilotrif)	• 2013: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions • 2016: Second line for patients with metastatic squamous NSCLC • 2018: First line for patients with nonresistant EGFR variants other than exon 19 or exon 21 NSCLC	• 2013: therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit (Qiagen) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
Alectinib (Alecensa)	• 2015: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib • 2017: Patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test	• 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: Ventana ALK (D5F3) CDx Assay • 2020: FoundationOne Liquid CDx
Amivantamab-vmjw (Rybrenant)	• 2021: adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy	• 2021: Guardant360 CDx • 2021: Oncomine™ Dx Target Test
Atezolizumab (Tecentriq)	• 2020: First-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA approved test, with no EGFR or ALK genomic tumor aberrations. o in combination with bevacizumab, paclitaxel, and carboplatin, for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations	• 2020: Ventana PD-L1

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
	○ in combination with paclitaxel protein-bound and carboplatin for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations ○ for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy.	
Brigatinib (Alunbrig)	• 2020: Treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test	• 2020: Vysis ALK Break Apart FISH Probe Kit
Capmatinib (Tabrecta)	• 2020: Metastatic NSCLC whose tumors have a mutation that leads to *MET* exon 14 skipping as detected by an FDA-approved test.	• 2020: FoundationOne CDx™ • 2021: FoundationOne Liquid CDx™
Cemiplimab-rwlc (Libtayo)	• 2022: First-line treatment of patients with advanced NSCLC (locally advanced who are not candidates for surgical resection or definitive chemoradiation or metastatic) whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] ≥ 50%) as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations	• 2021: PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)
Ceritinib (Zykadia)	• 2014: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib • 2017: First line for patients with ALK-positive metastatic NSCLC	• 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: VENTANA ALK (D5F3) CDx Assay
Crizotinib (Xalkori)	• 2011: First line for patients with ALK -positive metastatic NSCLC	• 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) • 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)
Crizotinib (Xalkori)	• 2016: Patients with ROS1-positive metastatic NSCLC	• 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)
Dacomitinib (Vizimpro)	• 2018: First line for patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitutions	• 2018: therascreen EGFR RGQ PCR Kit • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
Dabrafenib (Tafinlar) plus trametinib (Mekinist)	• 2017: Used in combination for treatment of patients with metastatic NSCLC with BRAF V600E variant	• 2017: Oncomine™ Dx Target Test

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
		• 2017: FoundationOne CDx™ (Foundation Medicine)
Entrectinib (Rozlytrek)	• 2019: o Adult patients with metastatic NSCLC whose tumors are ROS1-positive o Adult and pediatric patients 12 years of age and older with ▪ solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, ▪ are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy	• 2022: FoundationOne CDx™ (Foundation Medicine)
Erlotinib (Tarceva)	• 2020: First-line treatment in combination with ramucirumab (Cyramza) for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions • 2013: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions • 2010: Maintenance for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy • 2004: Second line for patients with locally advanced or metastatic NSCLC	• 2013: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) • 2016: cobas® EGFR Mutation Test v2 (tissue or blood test) (Roche Diagnostics) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2020: FoundationOne® Liquid CDx • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
Gefitinib (Iressa)	• 2015: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions • 2003: Second line for patients with locally advanced or metastatic NSCLC	• 2015: therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit • 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) • 2020: cobas® EGFR Mutation Test v2 (tissue or plasma) (Roche Diagnostics) • 2020: FoundationOne® Liquid CDx • 2021: ONCO/Reveal Dx Lung & Colon

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
		Cancer Assay (O/RDx-LCCA)
Larotrectinib (Vitrakvi)	• 2018: Adult and pediatric patients with solid tumors that o have a NTRK gene fusion without a known acquired resistance mutation, o are metastatic or where surgical resection is likely to result in severe morbidity, and o have no satisfactory alternative treatments or that have progressed following treatment	• 2020: FoundationOne CDx® (solid tumors, NTRK1/2/3 fusions)
Lorlatinib (Lorbrena)	• 2018: Patients with ALK-positive metastatic NSCLC whose disease has progressed on: o crizotinib and at least 1 other ALK inhibitor for metastatic disease; or o alectinib as the first ALK inhibitor therapy for metastatic disease; or o ceritinib as the first ALK inhibitor therapy for metastatic disease	• 2021: Ventana ALK (D5F3) CDx Assay
Mobocertinib (Exkivity)	• 2021: Adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy	• 2021: Oncomine Dx Target Test
Nivolumab (Opdivo) in combination with Ipilimumab (Yervoy)	• 2020: o adult patients with metastatic NSCLC expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab o adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy o patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.	• 2020: PD-L1 IHC 28-8 PharmDx
Osimertinib (Tagrisso)	• 2015: Second line for patients with metastatic NSCLC whose tumors have EGFR T790M variants as detected by an FDA-approved test, who have not responded to EGFR-blocking therapy • 2018: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R variants • 2019: EGFR exon 19 deletion and EGFR exon 21 L858R alterations • 2020: adjuvant therapy after tumor resection in adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test	• 2015-2020: cobas® EGFR Mutation Test v2 (tissue or plasma • 2017-2019: FoundationOne CDx™ (Foundation Medicine) • 2020: Guardant360 CDx • 2020: FoundationOne® Liquid CDx
Pembrolizumab (Keytruda)	• 2018: Monotherapy for the treatment of patients with metastatic NSCLC whose tumors express PD-L1	• 2018: PD-L1 IHC 22C3 pharmDx

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
	(TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA • 2020: For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options	• 2020: FoundationOne CDx (TMB)
Pralsetinib (Gavreto)	• 2020: Adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test	• 2020: Oncomine Dx Target Test
Selpercatinib (Retevmo)	• 2020: Adult patients with metastatic RET fusion-positive NSCLC	• 2022: Oncomine Dx Target Test
Sotorasib (Lumakras)	• 2021: Adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least 1 prior systemic therapy	• 2021: Therascreen KRAS RGQ PCR kit • 2021: Guardant360 CDx
Tepotinib (Tepmetko)	• 2021: Adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations.	• No approved companion diagnostic
Fam-trastuzumab deruxtecan-nxki (Enhertu)	• 2022: Adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy	• 2022: Oncomine Dx Target Test • 2022: Guardant360 CDx

Sources: U.S. Food and Drug Administration (2022)[13]; U.S. Food and Drug Administration (n.d.)[14]
ALK: anaplastic lymphoma kinase; CDx: companion diagnostic; *EGFR*: epidermal growth factor receptor; ERBB2: erythroblastic oncogene B 2 receptor tyrosine kinase; FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; MET: mesenchymal-epithelial transition; NSCLC: non-small-cell lung cancer; NTRK neurotrophic receptor tyrosine kinase; PCR: polymerase chain reaction.

Rationale

Background

Non-Small-Cell Lung Cancer

Treatment options for non-small-cell lung cancer (NSCLC) depend on disease stage and include various combinations of surgery, radiotherapy, systemic therapy, and best supportive care. Unfortunately, in up to 85% of cases, cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. Also, up to 40% of patients with NSCLC present with metastatic disease.[1] When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and 1-year survival of 30% to 45%.[2,3] The identification of specific, targetable oncogenic "driver mutations" in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology.

EGFR Gene

EGFR, a receptor tyrosine kinase (TK), is frequently overexpressed and activated in NSCLC. Drugs that inhibit EGFR signaling either prevent ligand binding to the extracellular domain (monoclonal antibodies) or inhibit intracellular TK activity (small-molecule tyrosine kinase inhibitors [TKIs]). These

targeted therapies dampen signal transduction through pathways downstream to the EGFR, such as the RAS/RAF/MAPK cascade. RAS proteins are G proteins that cycle between active and inactive forms in response to stimulation from cell surface receptors, such as EGFR, acting as binary switches between cell surface EGFR and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

EGFR Gene Variants

Somatic variants in the tyrosine kinase domain of the *EGFR* gene, notably small deletions in exon 19 and a point mutation in exon 21 (L858R, indicating substitution of leucine by arginine at codon position 858) are the most commonly found *EGFR* variants associated with sensitivity to EGFR tyrosine kinase inhibitors (TKIs; afatinib, erlotinib, gefitinib). These variants are referred to as sensitizing variants. Almost all patients who initially respond to an EGFR TKI experience disease progression. The most common of these secondary variants, called resistance variants, involves the substitution of methionine for threonine at position 790 (T790M) on exon 20.

EGFR Variant Frequency

Fang et al (2013) reported *EGFR* variants (all L858R) in 3 (2%) of 146 consecutively treated Chinese patients with early-stage squamous cell carcinoma (SCC).[4,] In a separate cohort of 63 Chinese patients with SCC who received erlotinib or gefitinib as second- or third-line treatment (63% never-smokers, 21% women), *EGFR* variant prevalence (all exon 19 deletion or L858R) was 23.8%.

In a comprehensive analysis of 14 studies involving 2880 patients, Mitsudomi et al (2006) reported *EGFR* variants in 10% of men, 7% of non-Asian patients, 7% of current or former smokers, and 2% of patients with nonadenocarcinoma histologies.[5,] Eberhard et al (2005)[6,] observed *EGFR* variants in 6.4% of patients with SCC and Rosell et al (2009)[7,] observed *EGFR* variants in 11.5% of patients with large cell carcinomas. Both studies had small sample sizes.

In 2 other studies, the acquired *EGFR* T790M variant has been estimated to be present in 50% to 60% of TKI-resistant cases in approximately 200 patients.[8,9,]

ALK Gene

ALK is a TK that, in NSCLC, is aberrantly activated because of a chromosomal rearrangement that leads to a fusion gene and expression of a protein with constitutive TK activity that has been demonstrated to play a role in controlling cell proliferation. The *EML4-ALK* fusion gene results from an inversion within the short arm of chromosome 2.

The *EML4-ALK* rearrangement ("*ALK*-positive") is detected in 3% to 6% of NSCLC patients, with the highest prevalence in never-smokers or light ex-smokers who have adenocarcinoma.

BRAF Gene

RAF proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. In this pathway, the *BRAF* gene is the most frequently mutated in NSCLC, in 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants.[10,] Most *BRAF* variants occur more frequently in smokers.

ROS1 Gene

ROS1 codes for a receptor TK of the insulin receptor family and chromosomal rearrangements result in fusion genes. The prevalence of *ROS1* fusions in NSCLC varies from 0.9% to 3.7%.[10,] Patients with *ROS1* fusions are typically never-smokers with adenocarcinoma.

KRAS Gene

The *KRAS* gene (which encodes RAS proteins) can harbor oncogenic variants that result in a constitutively activated protein, independent of signaling from the EGFR, possibly rendering a tumor

resistant to therapies that target the EGFR. Variants in the *KRAS* gene, mainly codons 12 and 13, have been reported in 20% to 30% of NSCLC, and occur most often in adenocarcinomas in heavy smokers.

KRAS variants can be detected by direct sequencing, PCR technologies, or NGS.

EGFR, *ALK*, *ROS1*, and *KRAS* driver mutations are considered to be mutually exclusive.

HER2 Gene

Human epidermal growth factor receptor 2 (*HER2*) is a member of the HER (EGFR) family of TK receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. *HER2* is expressed in approximately 25% of NSCLC. *HER2* variants are detected mainly in exon 20 in 1% to 2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.[10,]

RET Gene

RET (rearranged during transfection) is a proto-oncogene that encodes a receptor TK growth factor. Translocations that result in fusion genes with several partners have been reported.[10,] *RET* fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas.[10,]

MET Gene

MET alteration is one of the critical events for acquired resistance in *EGFR*-mutated adenocarcinomas refractory to EGFR TKIs.[10,]

NTRK Gene Fusions

NTRK gene fusions encode tropomyosin receptor kinase fusion proteins that act as oncogenic drivers for solid tumors including lung, salivary gland, thyroid, and sarcoma. It is estimated that NTRK gene fusions occur in 0.2% of patients with NSCLC and do not typically overlap with other oncogenic drivers.[11,]Testing for NTRK gene fusions is addressed separately in evidence review 5.01.31.

PD-1/PD-L1

Programmed cell ligand-1 (PD-L1) is a transmembrane protein expressed on the surface of multiple tissue types, including many tumor cells. Blocking the PD-L1 protein may prevent cancer cells from inactivating T cells.

Tumor Mutational Burden

Tumor mutational burden, a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple tumor types, including lung cancer.[12,]

Targeted Treatment and Immunotherapy

FDA-approved targeted treatments and immunotherapies for the variants described above are summarized in Table 2. (Note this information is current as of October 17, 2022. FDA maintains a list of oncology drug approval notifications at https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.)

Table 2. Targeted Treatments and Immunotherapy for Non-Small-Cell Lung Cancer

Target	FDA-Approved Therapies
EGFR	• Gefitinib (Iressa), • Erlotinib (Tarceva) alone or in combination with ramucirumab (Cyramza) • Afatinib (Gilotrif) • Osimertinib (Tagrisso) • Dacomitinib (Vizimpro) • Amivantamab-vmjw (Rybrenant) • Mobocertinib (Exkivity)
ALK	• Crizotinib (Xalkori)

Target	FDA-Approved Therapies
	• Ceritinib (Zykadia) • Alectinib (Alecensa) • Brigatinib (Alunbrig) • Lorlatinib (Lorbrena)
BRAF	• Dabrafenib (Tafinlar) alone or in combination with trametinib (Mekinist)
ROS1	• Crizotinib (Xalkori) • Entrectinib (Rozlytrek)
KRAS	• Sotorasib (Lumakras)
HER2 (ERBB2)	• Fam-trastuzumab deruxtecan-nxki (Enhertu)
RET	• Selpercatinib (Retevmo) • Pralsetinib (Gavreto)
MET	• Capmatinib (Tabrecta) • Tepotinib (Tepmetko)
NTRK[1]	• Larotrectinib (Vitrakvi) • Entrectinib (Rozlytrek)
PD-L1	• Pembrolizumab (Keytruda) • Nivolumab (Opdivo) in combination with ipilimumab (Yervoy) • Atezolizumab (Tecentriq) • Cemiplimab-rwlc (Libtayo)

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Somatic Biomarker Testing Using Tissue Biopsy to Select Targeted Therapy or Immunotherapy for Advanced-Stage Non-Small-Cell Lung Cancer

Clinical Context and Test Purpose

The purpose of identifying targetable oncogenic “driver mutations” in patients who have non-small-cell lung cancer (NSCLC) is to inform a decision whether patients should receive a targeted therapy versus another systemic therapy. Patients who present with advanced disease or recurrence following initial definitive treatment typically receive systemic therapy. Traditionally, systemic therapy was cytotoxic chemotherapy. However, certain patients may be good candidates for treatment with targeted therapies or immunotherapy. The goal of targeted therapies is to

preferentially kill malignant cells without significant damage to normal cells so that there is improved therapeutic efficacy along with decreased toxicity.

The question addressed in this evidence review is this: Does testing for epidermal growth factor receptor (*EGFR*), *BRAF*, *KRAS*, or *HER2* variants; *ALK*, *ROS*, or *RET* rearrangements; or *MET* alterations improve outcomes in individuals with advanced-stage NSCLC who are being considered for targeted therapy or immunotherapy?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with advanced NSCLC who are being considered for targeted therapy.

Interventions
The intervention of interest is testing for somatic genome alterations known as "driver mutations," specifically *EGFR*, *BRAF*, *KRAS*, *HER2* variants; *ALK*, *ROS*, or *RET* rearrangements; or *MET* alterations.

Comparators
The following practice is currently being used to target therapy for advanced-stage NSCLC: standard management without testing for driver mutations. Standard management consists primarily of chemotherapy, although some patients are candidates for immunotherapy.

Outcomes
Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved QOL associated with receiving a more effective and less cytotoxic targeted therapy than chemotherapy in those with driver mutations. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those without driver mutations.

Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those with driver mutations; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective targeted treatment and delay in initiation of chemotherapy in those without driver mutations.

Due to the poor prognosis of advanced NSCLC, the duration of follow-up for the outcomes of interest is 6 months and 1 year.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as

panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

Review of Evidence

The evidence is presented below, by variant (*EGFR*, *ALK*, *BRAF*, *ROS1*, *KRAS*, *HER2*, *RET*, *MET)* and by recommended therapy.

EGFR Gene Variants

FDA-Approved Companion Diagnostic Tissue Tests for *EGFR* Variants

Several tissue-based tests have been approved as companion diagnostics to detect *EGFR*-resistance variants (exon 19 deletions or exon 21 L858R substitutions) for at least 1 of the EGFR TKIs (afatinib, erlotinib, gefitinib, dacomitinib, or osimertinib): the therascreen EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit, cobas EGFR Mutation Test v1 and v2, Oncomine Dx Target Test, ONCO/Reveal Dx Lung & Colon Cancer Assay, and FoundationOne CDx (see Table 2). The cobas v2 test also is approved as a companion diagnostic to detect the T790M resistance variant to select patients for treatment with osimertinib. The Oncomine Dx Target Test is also approved as a companion diagnostic to detect *EGFR* exon 20 insertions to select patients for treatment with mobocertinib or amivantamab.

EGFR Tyrosine Kinase Inhibitors

Combined Analyses

A meta-analysis by Lee et al (2013), which evaluated 23 trials of erlotinib, gefitinib, and afatinib in patients with advanced NSCLC, reported improved progression-free survival (PFS) in *EGFR* variant-positive patients treated with EGFR TKIs in the first- and second-line settings and for maintenance therapy.[15,] Comparators were with chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings, respectively. Among *EGFR* variant-negative patients, PFS was improved using EGFR TKIs compared with placebo maintenance but not in the first- and second-line settings. Overall survival (OS) did not differ between treatment groups in either variant-positive or variant-negative patients. Statistical heterogeneity was not reported for any outcome.

A TEC Assessment (2007) evaluated *EGFR* variants and TKI therapy in advanced NSCLC.[16,] It concluded that there was insufficient evidence to permit conclusions about the clinical validity or utility of *EGFR* variant testing to predict erlotinib sensitivity or to guide treatment in patients with NSCLC. An updated Assessment (2010), with revised conclusions, indicated that *EGFR* variant testing has clinical utility in selecting or deselecting patients for treatment with erlotinib.[16,] Other meta-analyses have confirmed the PFS and OS results, and conclusions for *EGFR*-positive patients have been published.[17,16,18,19,20,]

Erlotinib

Systematic Reviews

Petrelli et al (2012) reported a meta-analysis (13 randomized trials) of 1260 patients with *EGFR*-mutated NSCLC who received TKIs for first-line, second-line, or maintenance therapy.[21,] The comparator was standard therapy. Overall, reviewers noted that the use of EGFR TKIs increased the chance of obtaining an objective response almost 2 fold compared with chemotherapy. Response rates were 70% versus 33% in first-line trials and 47% versus 28.5% in second-line trials. Tyrosine kinase inhibitors reduced the hazard of progression by 70% in all trials and by 65% in first-line trials; however, they did not improve OS.

Randomized Controlled Trials

The superiority of erlotinib over chemotherapy in the first-line setting was established in the ENSURE,[22,] EURTAC,[23,], and OPTIMAL[22,23,] RCTs. The 3 RCTs included 555 patients with stage IIIB or IV NSCLC. All reported clinically and statistically significant improvements in PFS (HR range, 0.16 to

0.37), but no improvements in OS with erlotinib versus chemotherapy. Grade 3 or greater adverse events and serious adverse events occurred in fewer patients in the erlotinib groups.

Many additional publications have provided data on *EGFR* variants in tumor samples obtained from NSCLC patients treated with erlotinib. Nine of these [4,24,-,31,] were nonconcurrent prospective studies of treatment-naive and previously treated patients who received erlotinib and were then tested for the presence or absence of variants. Four others were prospective, single-arm enrichment studies of variant-positive or wild-type patients treated with erlotinib. In 3 studies of *EGFR* variant-positive patients, the objective radiologic response was 40% to 70%, the median PFS was 8 to 14 months, and the median OS was 16 to 29 months.[5,32,33,] In patients with wild-type tumors, the objective radiologic response was 3.3%, PFS was 2.1 months, and OS was 9.2 months.[34,]

Gefitinib

Systematic Reviews

A Cochrane review by Sim et al (2018) compared the use of gefitinib with no therapy or chemotherapy as first-line, second-line, or maintenance therapy for NSCLC.[35,] The literature search was conducted in February 2017 and identified 35 RCTs (N=12,089 patients) for inclusion. For the general population of patients with NSCLC, gefitinib did not improve OS when given as first- or second-line therapy but did improve PFS when administered as maintenance therapy. In the subset of patients with *EGFR* variants, gefitinib improved PFS compared with first- and second-line chemotherapy and improved both OS and PFS when administered as maintenance therapy.

Randomized Controlled Trials

Three RCTs have compared gefitinib with chemotherapy in the first-line setting.[36,37,38,] The RCTs included 668 patients with stage IIIB or IV NSCLC and *EGFR*-sensitizing variants. All reported clinically and statistically significant improvement in PFS (HR range, 0.30 to 0.49) but no improvement in OS with gefitinib compared with chemotherapy. Grade 3 or greater adverse events occurred in fewer patients in the gefitinib groups. The Iressa Pan-Asia Study (IPASS) trial enrolled patients with and without *EGFR*-sensitizing variants. The investigators reported a significant interaction between treatment and *EGFR* variant status for PFS (interaction p<.001); PFS was longer for gefitinib in patients with *EGFR*-sensitizing variants and shorter for gefitinib in patients without *EGFR*-sensitizing variants. A 3-arm RCT compared a combination of chemotherapy plus gefitinib with chemotherapy alone and gefitinib alone.[37,] Patients in the combined treatment arm experienced longer OS compared with chemotherapy and gefitinib alone.

Wu et al (2017) conducted a post hoc subgroup analysis focusing on Asian patients in the IPASS trial who were randomized to gefitinib (n=88) or carboplatin/paclitaxel (n=98).[39,] The analysis found that patients with the *EGFR* variant who received gefitinib experienced longer PFS than patients receiving chemotherapy (HR, 0.5; 95% CI, 0.4 to 0.8).

Afatinib

Unlike erlotinib and gefitinib, which selectively inhibit EGFR, afatinib inhibits not only EGFR but also human epidermal growth factor receptor 2 (HER2) and HER4, and may have activity in patients with acquired resistance to TKIs. Such patients often harbor a T790M variant (substitution of threonine by methionine at codon 790) in *EGFR* exon 20. The efficacy and safety of afatinib were evaluated in the LUX-Lung series of studies.

LUX-Lung 3 was an RCT including 345 patients with stage IIIB or IV, *EGFR* variant-positive, lung adenocarcinoma who were previously untreated for advanced disease.[40,] Seventy-two percent of patients were Asian, 26% were white, and 90% (308 patients) had common *EGFR* variants (exon 19 deletion or L858R substitution variant in exon 21). Patients received afatinib or chemotherapy (cisplatin plus pemetrexed). In a stratified analysis of patients with common *EGFR* variants, the median PFS was 13.6 months for the afatinib group and 6.9 months for the chemotherapy group (HR,

0.47; 95% CI, 0.34 to 0.65; p=.001). The median PFS for the 10% of patients who had other *EGFR* variants was not reported, but the median PFS for the entire patient sample was 11.1 months in the afatinib group and 6.9 months in the chemotherapy group (HR, 0.58; 95% CI, 0.43 to 0.78; p=.001). The incidence of objective response in the entire patient sample was 56% in the afatinib group and 23% in the chemotherapy group (p=.001). With a median follow-up of 16.4 months, the median OS was not reached in any group; preliminary analysis indicated no difference in OS between the 2 treatment groups in the entire patient sample (HR, 1.12; 95% CI, 0.73 to 1.73; p=.60). Patients in the afatinib group reported greater improvements in dyspnea, cough, and global health status/QOL than those in the chemotherapy group.[41,] Grade 3 or higher diarrhea, rash, and paronychia (nail infection) occurred in 14%, 16%, and 11% of afatinib-treated patients, respectively, and in no patients in the chemotherapy group. Grade 3 or higher mucositis (primarily stomatitis) occurred in 9% of the afatinib group and 1% of the chemotherapy group.[40,] Similar results were reported by Wu et al (2014) in a phase 3 trial conducted in 364 Asian patients (Lux-Lung 6), which compared afatinib with gemcitabine plus cisplatin.[42,] Progression-free survival was 11.0 in the afatinib group and 5.6 months in the chemotherapy group (HR, 0.28; 95% CI, 0.20 to 0.39) and the response rates were 67% and 23%, respectively.

Three other published LUX-Lung studies evaluated patients with stage IIIB or IV lung adenocarcinoma who were previously treated for advanced disease, but design features limit interpretation of results.

- LUX-Lung 2 was a single-arm study (2012) of afatinib in 129 patients (87% Asian, 12% white) with *EGFR* variant-positive disease.[43,] Patients had been treated with chemotherapy but not with *EGFR*-targeted therapy; approximately half of the patients (enrolled after a protocol amendment) were chemotherapy-naive. Objective responses (primarily partial responses) were observed in 66% of 106 patients with common *EGFR* variants (exon 19 deletion or L858R) and in 39% of 23 patients with other *EGFR* variants. The median PFS was 13.7 months in patients with common *EGFR* variants and 3.7 months in patients with other *EGFR* variants (p not reported). Results for variant-negative patients were not reported.
- LUX-Lung 1 and LUX-Lung 4 enrolled patients who had progressed on previous treatment with erlotinib, gefitinib, or both for advanced disease. Neither study prospectively genotyped patients. In the LUX-Lung 1 double-blind RCT, 96 (66% Asian, 33% white) of 585 enrolled patients were *EGFR* variant-positive (76 common *EGFR* variant-positive).[44,] In this group, the median PFS was 3.3 months in the afatinib group and 1.0 month in the placebo group (HR, 0.51; 95% CI, 0.31 to 0.85; p=.009). In 45 variant-negative patients, the median PFS was 2.8 months in the afatinib group and 1.8 months in the placebo group, a statistically nonsignificant difference (p=.22), possibly due to small group sizes. LUX-Lung 4 was a single-arm study (2013) of afatinib in 62 Japanese patients.[45,] Objective responses occurred in 2 (5%) of 36 patients with common *EGFR* variants and in none of 8 patients with other *EGFR* variants (p>.05).

Osimertinib

In 2015, the U.S. Food and Drug Administration (FDA) granted accelerated approval to osimertinib for treatment of metastatic *EGFR* T790M variant-positive NSCLC patients who have progressed on or after EGFR TKI therapy.[46,] The therapy was approved with an FDA-approved companion test, the cobas EGFR Mutation Test v2, which is a blood-based genetic test to detect *EGFR* variants including the T790M variant. Approval was based on 2 multicenter, single-arm studies.[47,]

The osimertinib label describes the 2 studies.[46,] Eligible patients had metastatic *EGFR* T790M variant-positive NSCLC and had progressed on prior systemic therapy, including an EGFR TKI. Patients received osimertinib 80 mg once daily. The first study enrolled 201 patients; the second enrolled 210 patients. The major efficacy outcome measure of both trials was the objective response rate (ORR) assessed by a blinded, independent review committee. The median duration of follow-up was 4.2 months in the first study and 4.0 months in the second. The ORR was similar in the 2 studies. The

pooled ORR was 59% (95% CI, 54% to 64%); 0.5% achieved a complete response and 59% achieved a partial response. The most common adverse reactions were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%). Serious adverse reactions reported in 2% or more patients were pneumonia and pulmonary embolus. Fatal adverse reactions included the following: 4 patients with interstitial lung disease/pneumonitis; 4 patients with pneumonia, and 2 patients with cerebral vascular accident/cerebral hemorrhage.

One RCT (FLAURA; NCT02296125) has compared osimertinib with chemotherapy.[48,] Osimertinib was associated with clinically and statistically significantly prolonged PFS and higher response rates than chemotherapy and had lower rates of grade 3 and 4 adverse events. However, interstitial lung disease-like adverse events and QT prolongation were more common with osimertinib. Osimertinib received approval for the first-line treatment of NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations in 2018 based on this RCT. Another RCT (AURA3; NCT02151981) compared osimertinib with other EGFR TKIs (gefitinib or erlotinib) as first-line therapy.[49,] The results suggested a reduced risk for central nervous system progression with osimertinib compared with other TKIs. Osimertinib was granted full approval for T790M mutation-positive NSCLC in 2017 based on data from the AURA3 trial.

Dacomitinib

In 2018, the U.S. Food and Drug Administration approved dacomitinib (Vizimpro) for the first-line treatment of patients with unresectable, metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R substitution mutations.[50,] Approval was based on the multicenter, open-label, active controlled ARCHER 1050 (NCT01774721) RCT.[51,] The safety and efficacy of dacomitinib to gefitinib was established in 452 patients with no prior therapy for metastatic or recurrent disease with a minimum of 12 months disease-free after completion of systemic non-EGFR TKI-containing therapy. The trial demonstrated a significant improvement in PFS compared to gefitinib (14.7 vs. 9.2 months; HR, 0.59; 95% CI, 0.47 to 0.74; p<.0001). No improvements in the overall response rate or OS were observed. Serious adverse events occurred in 27% of patients, of which diarrhea ad interstitial lung disease were most common.

Mobocertinib

In 2021, the U.S. Food and Drug Administration granted accelerated approval to mobocertinib (Exkivity), an oral kinase inhibitor, for adult patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. Approval was based on Study 101 (NCT02716116), an international, nonrandomized, open-label, multicohort trial. Efficacy was evaluated in 114 patients.[52,] The main efficacy outcome, the overall response rate, was 28% (95% CI, 20% to 37%) with a median duration of response of 17.5 months (95% CI, 7.4 to 20.3). The most common adverse reactions were diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. Product labeling incudes a boxed warning for cardiac toxicity, interstitial lung disease/pneumonitis, diarrhea, and embryo-fetal toxicity.

Comparative Effectiveness of *EGFR*Tyrosine Kinase Inhibitors

As the previous sections have shown, erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib all have improved efficacy compared with chemotherapy, placebo, or alternative active therapy in patients who have NSCLC and *EGFR*-sensitizing variants and are well tolerated. Randomized controlled trials, as well as systematic reviews and meta-analyses of the RCTs, directly comparing the EGFR TKIs with each other and with chemotherapy, have been conducted.[53,-,59,]

The systematic reviews and meta-analyses included overlapping trials. Randomized controlled trials included in the reviews and analyses differed in study design, treatments compared, and line of treatment (first-, second-, or third-line). In general, patients who are EGFR-positive and treated with TKIs experienced longer PFS than patients treated with chemotherapy. Meta-analyses comparing

different TKIs reported inconsistent results, with some analyses finding various TKIs comparable and other analyses finding some TKIs more effective than others. Safety data were not consistently available among the RCTs, limiting adverse event comparisons among treatments.

Randomized Controlled Trials

Soria et al (2018) conducted a double-blind phase 3 trial comparing osimertinib with other TKIs (gefitinib or erlotinib) for the first-line treatment of patients with *EGFR*-positive advanced NSCLC.[60,] Median PFS was longer with osimertinib (18.9 months; 95% CI, 15.2 to 21.4 months) than with the other TKIs (10.2 months, 95% CI, 9.6 to 11.1 months; HR, 0.5, 95% CI, 0.4 to 0.6). Objective response rate did not differ significantly between osimertinib and the other TKIs. Follow-up was not long enough to adequately determine OS.

Two RCTs compared gefitinib with erlotinib in patients who had *EGFR*-sensitizing variants. Urata et al (2016) reported on a phase 3 RCT of 401 patients with *EGFR* variants randomized to gefitinib or erlotinib.[61,] The median PFS was 8.3 months (95% CI, 7.2 to 9.7 months) for patients receiving gefitinib and 10.0 months (95% CI, 8.5 to 11.2 months) for those receiving erlotinib. Rash was more common with erlotinib (18.1% vs. 2.2%) while both alanine aminotransferase elevation and aspartate aminotransferase elevation were more common with gefitinib (6.1% v.s 2.2% and 13.0% vs. 3.3%, respectively). Similarly, Yang et al (2017) reported a median PFS of 13.0 months for erlotinib and 10.4 months for gefitinib (HR, 0.81; 95% CI, 0.62 to 1.05) in 256 patients, with no differences in rates of grade 3 or 4 adverse events.[62,]

LUX-7 was a phase 2b, head-to-head trial of afatinib versus gefitinib for the treatment of first-line *EGFR* variant-positive (del19 and *L858R*) adenocarcinoma of the lung.[63,] LUX-7 randomized 319 patients in a 1:1 ratio to afatinib 40 mg/d or gefitinib 250 mg/d, stratified by variant type (del19 and L858R) and brain metastases (present vs. absent). In the overall population, PFS was significantly improved with afatinib than with gefitinib (HR, 0.73; 95% CI, 0.57 to 0.95; p=.02). Time-to-treatment failure also showed improvement in favor of afatinib (HR, 0.73; 95% CI, 0.58 to 0.92; p=.01). The ORR was significantly higher in the afatinib group (70% vs. 56%; p=.01). Several grade 3 or 4 adverse events were more common with afatinib than with gefitinib including diarrhea (13% vs. 1%) and rash (9% vs. 3%); liver enzyme elevations were more common with gefitinib (0% vs. 9%). Serious events occurred in 11% of patients in the afatinib group and 4% in the gefitinib group.

Immunotherapies

Erlotinb in Combination with Ramucirumab

In 2020, the FDA approved erlotinib in combination with ramucirumab (Cyramza), an antineoplastic agent and direct vascular endothelial growth factor (VEGF) receptor 2 antagonist, for the first-line treatment of metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 (L858R) mutations. Efficacy was established in the multinational, double-blind, placebo-controlled, multicenter RELAY RCT (NCT02411448).[64,65,] Median PFS was 19.4 months in the ramucirumab plus erlotinib arm compared with 12.4 months in the placebo plus erlotinib arm (HR, 0.59; 95% CI, 0.46 to 0.76; p<.0001). The objective response rate and median duration of response was 76% and 18.0 months for ramucirumab plus erlotinib compared with 75% and 11.1 months with placebo plus erlotinib. The most common adverse events were infection, hypertension, stomatitis, proteinuria, alopecia, epistaxis, and peripheral edema.

Amivantamab-vmjw

In 2021, the U.S. FDA granted accelerated approval to amivantamab-vmjw (Rybrevant), a bispecific antibody directed against EGFR and MET receptors, for adult patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy.[66,] Approval was based on CHRYSALIS (NCT02609776), a multicenter, nonrandomized, open-label, multicohort trial.[67,] Efficacy was evaluated in 81 patients who exhibited an overall response rate and median duration of response of 40% (95% CI, 29% to 51%) and 11.1

months (95% CI, 6.9 to not evaluable), respectively. The most common adverse reactions were rash, infusion-related reactions, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting.

Section Summary: *EGFR* Gene Variants

Several RCTs, nonconcurrent prospective studies, single-arm enrichment studies, and meta-analyses of RCTs have demonstrated that patients with *EGFR*-sensitivity variants (exon 19 deletion or L858R substitution variant in exon 21) benefit from erlotinib, gefitinib, dacomitinib, or afatinib therapy and patients with *EGFR*-resistance variant (T790M) benefit from osimertinib. Patient populations in these studies primarily had adenocarcinoma. Currently, there is little evidence to indicate that *EGFR* variant testing can guide treatment selection in patients with squamous cell histology. Patients who are found to have wild-type tumors are unlikely to respond to erlotinib, gefitinib, or afatinib. These patients should be considered candidates for alternative therapies. Recent studies have also demonstrated that patients with *EGFR* exon 20 insertion mutations may benefit from immunotherapy, including amivantamab-vmjw following disease progression or ramucirumab in combination with erlotinib as first-line therapy.

ALK Gene Rearrangements

ALK gene rearrangements most often consist of an inversion in chromosome 2, which leads to fusion with the echinoderm microtubule-associated protein like 4 (*EML4*) gene and a novel fusion oncogene *EML4-ALK*. This inversion causes abnormal expression and activation of ALK tyrosine kinase.[68,] *ALK* rearrangements occur in 3% to 6% of NSCLC.

FDA-Approved Companion Diagnostic Tissue Tests for *ALK* Rearrangements

Several methods are available to detect *ALK* gene rearrangements or the resulting fusion proteins in tumor specimens including FISH, immunohistochemistry, reverse transcription-PCR of cDNA, and NGS.

Companion diagnostic tests have been FDA-approved to select patients with NSCLC for treatment with the ALK inhibitors ceritinib, alectinib, brigatinib, crizotinib, and lorlatinib (see Table 2).

ALK Inhibitors

Crizotinib

The accelerated approval of crizotinib by the FDA was based on phase 1 and 2 trials in which crizotinib showed marked antitumor activity in patients with *ALK*-positive advanced NSCLC, with an ORR of 60% and PFS range from 7 to 10 months.[69,] These results were confirmed in 2 subsequent phase 3 trials.

A phase 3, open-label trial randomized 347 patients with previously treated, locally advanced, or metastatic *ALK*-positive lung cancer to oral crizotinib twice daily (n=173) or chemotherapy (n=174) every 3 weeks. All patients had received 1 platinum-based chemotherapy regimen before the trial. The extent of metastatic disease was 95% and 91% in patients in the crizotinib and chemotherapy groups, respectively, and tumor histology was adenocarcinoma in 95% and 94%, respectively. The primary endpoint was PFS. Patients in the chemotherapy group who experienced progressive disease were allowed to cross over to crizotinib as part of a separate study. The median PFS was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group (HR for progression or death with crizotinib, 0.49; 95% CI, 0.37 to 0.64; p<.001). Partial response rates with crizotinib were 65% (95% CI, 58% to 72%) and 20% (95% CI, 14% to 26%) with chemotherapy (p<.001). Interim analysis of OS showed no significant improvement with crizotinib compared with chemotherapy (HR for death in the crizotinib group, 1.02; 95% CI, 0.68 to 1.54; p=.54). The median follow-up for OS was 12.2 in the crizotinib group and 12.1 months in the chemotherapy group. Patients reported greater reductions in lung cancer symptoms and greater improvement in global QOL with crizotinib than with chemotherapy.

A phase 3, open-label trial compared crizotinib and chemotherapy in 343 previously untreated patients with *ALK*-positive advanced nonsquamous NSCLC.[70,] Patients were randomized to oral crizotinib twice daily or pemetrexed plus cisplatin or carboplatin every 3 weeks for up to 6 cycles. If there was disease progression for patients receiving chemotherapy, crossover to crizotinib was allowed. Progression-free survival was the primary endpoint; PFS was 10.9 months compared with 7.0 months for the groups that received crizotinib and chemotherapy, respectively (HR for progression or death with crizotinib, 0.45; 95% CI, 0.35 to 0.60; p<.001) and ORRs (complete and partial responses) were 74% and 45%, respectively (p<.001). The median OS was not reached in either group. The probability of 1-year survival with crizotinib was 84% and 79% with chemotherapy. Crizotinib was associated with greater patient-reported reductions in lung cancer symptoms and greater improvements in QOL.

Other ALK Inhibitors

Ceritinib has demonstrated superior efficacy concerning PFS when compared with chemotherapy in both the first-line and second-line (following crizotinib) settings in the ASCEND-4 and ASCEND-5 RCTs.[71,70,]

Alectinib was associated with response rates of approximately 50% in patients who had progressed on crizotinib in 2, phase 2 studies.[72,73,] Alectinib has also shown superior efficacy and lower toxicity when compared with crizotinib in the first-line setting in the ALEX and J-ALEX phase 3 RCTs.[74,75,]

Brigatinib has shown promise in early phase 1 and 2 studies with PFS of almost 13 months in patients with crizotinib-refractory disease.[76,77,] The FDA approval was granted to brigatinib in 2017 for the treatment of patients with *ALK*-positive NSCLC who have progressed on or are intolerant of crizotinib. Approval was based on an open-label, multicenter clinical trial that reported a durable overall response rate.[78,]

Lorlatinib received FDA approval in 2021 for first-line therapy of *ALK*-positive metastatic NSCLC based on Study B7461006 (NCT3052608), which randomized patients 1:1 to receive either lorlatinib or crizotinib.[79,80,] Lorlatinib demonstrated an improvement in PFS, with a hazard ratio of 0.28 (95% CI, 0.19 to 0.41; p<.001). Previously, lorlatinib received accelerated approval in 2018 for the second- or third-line treatment of *ALK*-positive metastatic NSCLC.

Section Summary: *ALK* Gene Rearrangements

Crizotinib was granted accelerated approval by the FDA in 2011 for patients with locally advanced or metastatic NSCLC, based on ORRs observed in 2, single-arm trials. Two subsequent, phase 3 trials have shown superior PFS and tumor response rates and improved QOL in patients with crizotinib versus chemotherapy, in both previously untreated and untreated *ALK*-positive advanced NSCLC. Other ALK inhibitors receiving FDA-approval include ceritinib, alectinib, brigatinib, and lorlatinib. Companion diagnostic tissue tests have been FDA-approved to select patients with NSCLC for treatment with these therapies.

BRAF Gene Variants

FDA-Approved Companion Diagnostic Tissue Tests for *BRAF* Variants

BRAF variants are detected by PCR sequencing or NGS methods. The Oncomine Dx Target Test and FoundationOne CDx were FDA-approved in 2017 as companion diagnostic tests to detect *BRAF* V600E variants to aid in selecting NSCLC patients for treatment with combination dabrafenib (Tafinlar) and trametinib (Mekinist) therapy.

BRAF Inhibitors

Dabrafenib and Trametinib

The dabrafenib and trametinib product labels describe the results of an open-label, multicenter study of patients enrolled in 3 cohorts: cohorts A and B had received at least 1 previous platinum-based chemotherapy regimen with demonstrated disease progression but no more than 3 prior systemic regimens; cohort C could not have received prior systemic therapy for metastatic disease.[81,] Trial results for cohorts A,[82,] B,[83,] and C[84,] were reported by Planchard et al (2016, 2017). Cohort A (n=78) received dabrafenib; cohorts B (n=57) and C (n=36) received dabrafenib and trametinib combination therapy. The response rate for dabrafenib monotherapy in 78 patients who had progressed on chemotherapy was 33% at 11 months median follow-up while the response rate for 19 patients (17 of whom had progressed on chemotherapy) treated with vemurafenib monotherapy was 42% at 8 weeks. Response rates for dabrafenib and trametinib combination therapy were higher than 60% in patients who had progressed on prior treatment and those who were treatment-naive. Toxicities were similar to those seen in melanoma patients taking BRAF or MEK inhibitors. Squamous cell carcinomas and other dermatological side effects were reported.

Case reports have also documented response to vemurafenib in patients with NSCLC and a *BRAF* variant.[85,86,]

Section Summary: *BRAF* Gene Variants

The FDA has approved companion diagnostics for detecting *BRAF* variants to aid in selecting NSCLC patients for treatment with combination BRAF and MEK inhibitors, dabrafenib and trametinib. The clinical validity of the companion diagnostic was established in the Summary of Safety and Effectiveness Data document. The FDA expanded the indication for dabrafenib and trametinib to include the treatment of NSCLC patients whose tumors have a *BRAF* V600E variant based on a multicenter, single-arm study that included a cohort of 57 patients who had progressed on prior therapy and a cohort of 36 treatment-naive patients. Dabrafenib and trametinib combination therapy were effective in patients with a *BRAF* V600E variant, with a response rate of about 60% in both cohorts. Lower response rates were reported in other nonrandomized studies of BRAF inhibitor monotherapy in patients who had previously progressed on prior treatments.

ROS1 Gene Rearrangements

FDA-Approved Companion Diagnostic Tissue Tests for *ROS1* Rearrangements

Several methods are available to detect *ROS1* translocations including FISH, immunohistochemistry, quantitative real-time reverse transcription-PCR, and some NGS panels. The Oncomine Dx Target Test was FDA-approved in 2017 as a companion diagnostic to detect fusions in *ROS1* to aid in selecting NSCLC patients for treatment with crizotinib (Xalkori). The Oncomine test is an NGS oncology panel that detects, among other variants, fusions in *ROS1* from RNA isolated from FFPE tumor tissue samples. The FoundationOne CDx test was FDA-approved in 2022 to select patients for treatment with entrectinib (Rozlytrek).In 2022, FoundationOne CDx received FDA approval as a companion diagnostic to detect fusions in *ROS1* to aid in selecting NSCLC patients for treatment with entrectinib (Rozlytrek).

Tyrosine Kinase Inhibitors

Crizotinib

In 2016, after an expedited review, the FDA expanded the indication for crizotinib to include the treatment of patients whose metastatic NSCLC tumors have a *ROS1* rearrangement. The approval was based on a 2014 multicenter, single-arm study that enrolled 50 patients with advanced NSCLC who tested positive for *ROS1* rearrangement.[87,] The study assessed an expansion cohort of the phase 1 PROFILE 1001 Trial. Patients were given oral crizotinib (250 mg twice daily) in continuous 28-day cycles; the median duration of treatment was 65 weeks. Nonrandomized and observational studies of crizotinib have shown response rates of greater than 70% in patients with *ROS1* rearrangements, the majority of whom had progressed on prior therapy.[87,88,] A companion *ROS1* biomarker diagnostic

test was not approved at the time of the crizotinib indication expansion. However, the Oncomine Dx Target Test was FDA-approved in 2017 as a companion diagnostic to detect fusions in *ROS1* to aid in selecting NSCLC patients for treatment with crizotinib (Xalkori).

Entrectinib

In 2019, entrectinib (Rozlytrek) received accelerated approval for adults with metastatic, *ROS1*-positive NSCLC. Drilon et al (2020) conducted an analysis of 53 patients with *ROS-1* fusion-positive NSCLC enrolled in 1 of 3 multicenter, single-arm, trials: ALKA, STARTRK-1, and STARTRK-2.[89,] At median follow-up of 15.5 months (interquartile range 13.4 to 20.2), 41 of 53 patients had an objective response (77%; 95% CI 64% to 88%), with a median duration of response of 24.6 months (95% CI 11.4 to 34.8). In the safety-evaluable population, 46 (34%) of 134 patients had grade 3 or 4 treatment-related adverse events. There were no treatment-related deaths.

Section Summary: *ROS1* Gene Rearrangements

The FDA has approved companion diagnostics for detecting *ROS1* gene rearrangements to aid in selecting NSCLC patients for treatment with crizotinib and entrectinib. The clinical validity of the companion diagnostic was established in the Summary of Safety and Effectiveness Data document. The FDA expanded the indication for crizotinib to include the treatment of patients whose tumors have a *ROS1* rearrangement based on a multicenter, single-arm study including 50 patients, the majority of whom had progressed on prior therapy. Crizotinib was effective in patients with *ROS1* rearrangements, with a response rate of about 70%. In an analysis of 53 patients with *ROS-1* fusion-positive NSCLC enrolled in 3 clinical trials of entrectinib, the ORR was 77%, with a median duration of response of 24.6 months.

KRAS Gene Variants

FDA-Approved Companion Diagnostic Tissue Tests for *KRAS* Variants

KRAS variants can be detected by direct sequencing, PCR technologies, or NGS. In 2021, the FDA approved therascreen KRAS RGQ PCR Kit to select patients for treatment with the KRAS inhibitor, sotorasib (Lumakras), based on the presence of *KRAS* G12C mutations.

RAS Inhibitor

Sotorasib

Skoulidis et al (2021) reported results of a phase 2, open-label trial of sotorasib in patients with KRAS variant NSCLC.[90,] Presence of the *KRAS* alteration in tissue was confirmed on central laboratory testing with the use of the therascreen KRAS RGQ PCR Kit. Among 124 patients evaluated for the primary outcome, 4 (3.2%) had a complete response and 42 (33.9%) had a partial response, with an acceptable safety profile. Median duration of response was 11.1 months (95% CI: 6.9 to not evaluable). Median PFS and OS were 6.8 months (95% CI, 5.1 to 8.2) and 12.5 months (95% CI, 10.0 to not evaluable), respectively.

EGFR Tyrosine Kinase Inhibitors

Data on the role of *KRAS* variants in NSCLC and response to erlotinib are available from post hoc analyses of phase 3 trials of TKIs in patients with wild-type (nonmutated) versus *KRAS*-mutated lung tumors;[33,91,6,92,] phase 2 trials;[29,32,31,] retrospective single-arm studies;[93,94,] and meta-analyses.[95,96,97,] To date, no EGFR TKIs have received FDA-approval for *KRAS*-positive NSCLC.

Anti-*EGFR* Monoclonal Antibodies

Two, phase 3 trials (BMS099, FLEX) investigated platinum-based chemotherapy with and without cetuximab in the first-line setting for advanced NSCLC. Subsequently, investigations of *KRAS* variant status and cetuximab treatment were performed for both trials.

In the multicenter, phase 3 BMS099 trial (2010), 676 chemotherapy-naive patients with stage IIIB or IV NSCLC were assigned to taxane and carboplatin with or without cetuximab.[98,] The primary

endpoint was PFS; secondary endpoints were overall response rate, OS, QOL, and safety. The addition of cetuximab did not significantly improve PFS; however, there was a statistically significant improvement in overall response rate in the cetuximab group. The trend in OS favoring cetuximab was not statistically significant. A post hoc correlative analysis was conducted to identify molecular markers for the selection of patients most likely to benefit from cetuximab.[99,] Of the original 676 enrolled patients, 202 (29.9%) had tumor samples available for *KRAS* testing. *KRAS* variants were present in 35 (17%) patients. Among patients with wild-type *KRAS*, OS was similar for the cetuximab-containing arm (n=85) and the chemotherapy-alone arm (n=82) (HR, 0.93; 95% CI, 0.67 to 1.30; p=.68; median survival, 9.7 months and 9.9 months, respectively). Among patients with *KRAS* variants, OS was similar between the cetuximab-containing arm (n=13) and the chemotherapy-alone arm (n=22) (HR, 0.91; 95% CI, 0.45 to 2.07; p=.93; median survival, 16.8 months and 10.8 months, respectively). Overall, the study showed no significant treatment-specific interactions for the presence of *KRAS* variants and outcomes evaluated; treatment differences favoring the addition of cetuximab in the *KRAS*-mutated subgroup were consistent with those observed in the wild-type *KRAS* subgroup and in the overall study population. The authors concluded that the results did not support an association between *KRAS* variant status and lack of cetuximab benefit. However, the results should be interpreted with caution due to small subgroup sample sizes and the retrospective nature of the analysis.

In the open-label, randomized, phase 3 FLEX trial (2009), 1125 chemotherapy-naive patients with stage III or IV, NSCLC were randomized to chemotherapy plus cetuximab (n=557) or chemotherapy alone (n=568).[100,] The primary endpoint was OS. Patients who received chemotherapy plus cetuximab survived longer than those who received chemotherapy only (median OS, 11.3 months vs. 10.1 months, respectively; HR for death, 0.87; 95% CI, 0.76 to 1.00; p=.04). Subsequently, *KRAS* variant testing was performed on archived tumor tissue of 395 (35%) of 1125 patients.[101,] *KRAS* variants were detected in 75 (19%) tumors. Among patients with mutated *KRAS*, the median OS in the cetuximab-containing (n=38) and chemotherapy-alone arms (n=37) was similar (8.9 months vs. 11.1 months, respectively; HR, 1.00; 95% CI, 0.60 to 1.66; p=1.0). Among patients with wild-type *KRAS*, the median OS in the cetuximab-containing (n=161) and chemotherapy-alone arms (n=159) was similar (11.4 months vs. 10.3 months, respectively; HR, 0.96; 95% CI, 0.75 to 1.23; p=.74). Progression-free survival also was similar in the cetuximab-containing and chemotherapy-alone arms in patients with mutated (HR, 0.97; 95% CI, 0.76 to 1.24) and wild-type (HR, 0.84; 95% CI, 0.50 to 1.40) *KRAS*. Response rates in the cetuximab-containing arm in patients with *KRAS*-mutated and wild-type tumors were 36.8% and 37.3%, respectively (p=.96). Overall, there was no indication that *KRAS* variant status was predictive of cetuximab effect in NSCLC.

MEK Inhibitors

Two RCTs have compared a MEK inhibitor (with or without chemotherapy) with chemotherapy alone in patients with *KRAS*-positive advanced NSCLC after progression with first-line therapy.[102,103,] MEK inhibitor therapy did not improve PFS compared with docetaxel alone; response rates were similar or marginally improved. Grade 3 or higher adverse events were more frequent with MEK inhibitor therapy compared with docetaxel.

Section Summary: *KRAS* Gene Variants

In a phase 2 trial of sotorasib conducted in 126 patients with *KRAS*G12C variant NSCLC with the use of the therascreen KRAS RGQ PCR Kit, overall response was 37.1% (95% CI 28.6% to 46.2%) with an acceptable safety profile. In an analysis of secondary endpoints, PFS was 6.8 months (95% CI 5.1 to 8.2) and OS was 12.5 months (95% CI, 10.0 to not evaluable).

Data on the role of *KRAS* variants in NSCLC and response to erlotinib are available from post hoc analysis of trials, observational studies, and meta-analyses. Although studies have shown that *KRAS* variants in patients with NSCLC confer a high level of resistance to TKIs, data are

insufficient to assess any additional benefit to *KRAS* testing beyond *EGFR* testing. To date, no EGFR TKIs have been approved for *KRAS*-positive NSCLC.

A lack of response to EGFR monoclonal antibodies has been established in metastatic colorectal cancer, and the use of these drugs is largely restricted to patients with wild-type *KRAS*. The expectation that *KRAS* variant status also would be an important predictive marker for cetuximab response in NSCLC has not been shown. In 2 randomized trials with post hoc analyses of *KRAS* variant status and use of cetuximab with chemotherapy, *KRAS* variants did not identify patients who would benefit from anti-EGFR antibodies, because outcomes with cetuximab were similar regardless of *KRAS* variant status.

Two RCTs have compared a MEK inhibitor with docetaxel in patients with *KRAS*-positive advanced NSCLC who had progression following first-line therapy. The MEK inhibitor did not improve PFS compared with docetaxel; the response rate was marginally improved. Grade 3 or higher adverse events were more frequent with the MEK inhibitors.

HER2 Gene Variants

FDA-Approved Companion Diagnostic Tissue Tests for *HER2* Variants

In August 2022, the Oncomine Dx Target Test was approved as a companion diagnostic to select patients for therapy with fam-trastuzumab deruxtecan-nxki (Enhertu).

Fam-trastuzumab deruxtecan-nxki

In August 2022, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu), an antibody-drug conjugate, for adult patients with unresectable or metastatic NSCLC whose tumors have activating human epidermal growth factor receptor 2 (HER2) mutations and who have received a prior systemic therapy.[104,] Approval was based on the DESTINY-Lung02 multicenter, blinded, and randomized dose-optimization trial which demonstrated an ORR of 58% (95% CI, 43% to 71%) and a median duration of response of 8.7 months (95% CI, 7.1 months to not estimable) among 52 patients. Most common grade 3 or 4 adverse events were anemia, fatigue, and nausea.

Section Summary: *HER2* Gene Variants

In a phase 2 trial of trastuzumab deruxtecan in 52 patients with *HER2* mutated NSCLC as detected with the Oncomine Dx Target Test, the overall response rate was 58% with an acceptable safety profile.

RET Gene Testing

FDA-Approved Companion Diagnostic Tissue Tests for *RET* Gene Testing

Oncomine Dx Target Test is FDA-approved as a companion diagnostic for pralsetinib and selpercatinib for the treatment of metastatic RET fusion-positive NSCLC.[13,]

RET Inhibitors

In May 2020, the FDA granted accelerated approval for selpercatinib for the treatment of adult patients with metastatic RET fusion-positive NSCLC. Approval was based on the overall response observed in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO) in patients whose tumors had RET alterations. The overall response rate among 105 patients who had previously received platinum-based chemotherapy was 64% (95% CI, 54% to 73%) compared to 85% (95% CI, 70% to 94%) among 39 previously untreated patients. Overall PFS was 16.5 months (95% CI, 13.7 months to not estimable). Most common grade 3 or 4 adverse events included hypertension and elevated alanine transaminase.[89,]In September 2022, the FDA approved the Oncomine Dx Target Test as a companion diagnostic for selpercatinib.

In September 2020, the FDA approved pralsetinib for the treatment of metastatic RET-fusion positive NSCLC along with the Oncomine Dx Target Test companion diagnostic. This indication was

approved under the FDA's Accelerated Approval program, based on data from the phase I/II ARROW study.The overall response rate among previously treated patients was 57% (95% CI, 46% to 68%) compared to 70% (95% CI, 50% to 86%) in previously untreated patients. PFS was 12.7 months (95% CI, 9.1 months to not estimable). Most common grade 3 or 4 adverse reactions were hypertension, pneumonia, and fatigue.[105,]

Section Summary: *RET* Gene Testing

The FDA has approved a companion diagnostic (Oncomine Dx Target Test) for treating metastatic *RET*-fusion positive NSCLC with pralsetinib or selpercatinib under accelerated approval based on studies of effect particularly among treatment naive patients (ORR 70% and 85%, respectively).

MET Gene Testing

FDA-Approved Companion Diagnostic Tissue Tests for *MET* Gene Testing

In 2020, FoundationOne CDx was FDA approved as a companion diagnostic for capmatinib for the treatment of NSCLC harboring *MET* with an exon 14 skipping alteration.[13,]

Capmatinib

In 2020, FDA approved the MET inhibitor capmatinib for treatment of adult patients with metastatic NSCLC whose tumors have an alteration that leads to MET exon 14 skipping. Approval was accelerated based on overall response rate and duration of response in the GEOMETRY mono-1 trial (NCT02414139)[106,]Among 97 patients with a MET exon 14 skipping alteration, PFS was 5.4 months (95% CI, 4.2 to 7.0) in previously treated individuals and 12.4 months (95% CI, 8.2 to not estimable) in previously untreated individuals. Corresponding median duration of response were 9.7 months (95% CI, 5.6 to 13.0) and 12.6 months (95% CI, 5.6 to not estimable), respectively. Most common adverse events were peripheral edema, nausea, vomiting, and increased blood creatinine levels.

Section Summary: *MET* Gene Testing

The GEOMETRY Mono-1 trial showed efficacy of capmatinib in patients with advanced NSCLC with a *MET* exon 14 skipping mutation, especially in treatment-naive patients (68% [95% CI, 48% to 84%]) and median duration of 12.6 months). Efficacy was also observed in pre-treated patients (overall response rate 41% [95% CI, 29% to 53%] and median duration of 9.7 months).

Immunotherapy for Advanced Non-Small-Cell Lung Cancer

Clinical Context and Test Purpose

The purpose of identifying PD-L1 expression and tumor mutational burden (TMB) in patients who have advanced NSCLC is to inform a decision whether patients should receive a immunotherapy versus another systemic therapy. Patients who present with advanced disease or recurrence following initial definitive treatment typically receive systemic therapy. Traditionally, systemic therapy was cytotoxic chemotherapy. Targeted treatments are ineffective in patients whose tumors lack genetic alterations such as EGFR, ALK, BRAF, and ROS1 variants (driver mutations). However, a subset of these patients may be good candidates for treatment with immunotherapy. The goal of immunotherapy is to preferentially kill malignant cells without significant damage to normal cells so that there is improved therapeutic efficacy along with decreased toxicity.
The question addressed in this evidence review is this: Does testing for PD-L1 and TMB improve the net health outcome in individuals with advanced-stage NSCLC who are being considered for immunotherapy?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with advanced NSCLC who are being considered for immunotherapy.

Interventions
The interventions of interest are testing for PD-L1 and TMB.

Comparators
The following practice is currently being used to target therapy for advanced-stage NSCLC: standard management without testing for PD-L1 or TMB. Standard management consists primarily of chemotherapy.

Outcomes
Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved QOL associated with receiving a more effective and less cytotoxic targeted therapy than chemotherapy. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those whose tumors do not express PD-L1.

Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those whose tumors express PD-L1; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective immunotherapy and delay in initiation of chemotherapy in those whose tumors do not express PD-L1.

Due to the poor prognosis of advanced NSCLC, the duration of follow-up for the outcomes of interest is 6 months and 1 year.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with NCCN recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

Review of Evidence
PD-L1 Testing

FDA Companion Diagnostic Tissue Tests for PD-L1
Companion diagnostic tests have been FDA-approved for PD-L1 testing for immunotherapy with cemiplimab-rwlc, atezolizumab, pembrolizumab, and the combination of nivolumab plus ipilimumab in patients with NSCLC (see Table 2).[13,]

Cemiplimab-rwlc
In February 2021, the U.S. FDA approved cemiplimab-rwlc (Libtayo) for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥ 50%).[107,] Approval was based on the EMPOWER-Lung 1 trial (NCT03088540), a multicenter, open-label trial that randomized 710 patients 1:1 to receive either cemiplimab-rwlc or platinum-based chemotherapy.[108,] Median OS was 22.1 months (95% CI, 17.7 to

not estimable) in the cemiplimab-rwlc arm compared to 14.3 months (95% CI, 11.7 to 19.2) in the chemotherapy arm (HR, 0.68; 95% CI, 0.53 to 0.87; p=.0022). Median PFS was 6.2 months with cemiplimab-rwlc versus 5.6 months with chemotherapy (HR, 0.59; 95% CI, 0.49 to 0.72; p<.0001). Corresponding ORRs were 37% (95% CI, 32% to 42%) versus 21% (95% CI, 17% to 25%), respectively. Most common adverse events were musculoskeletal pain, rash, anemia, fatigue, decreased appetite, pneumonia, and cough.[107,]

Atezolizumab

Herbst et al (2020) published results of a phase 3, open label RCT of atezolizumab compared to platinum-based chemotherapy in 572 patients with NSCLC who had not previously received chemotherapy and who had PD-L1 expression on at least 1% of tumor cells or at least 1% of tumor-infiltrating immune cells (NCT02409342).[109,] In the subgroup of patients with tumors who had the highest expression of PD-L1 (205 patients), the median OS was longer by 7.1 months in the atezolizumab group than in the chemotherapy group (20.2 months vs. 13.1 months; HR for death, 0.59; p=.01). Atezolizumab treatment resulted in significantly longer OS than platinum-based chemotherapy among patients with NSCLC with high PD-L1 expression, regardless of histologic type. Grade 3 or 4 adverse events occurred in 30.1% and 52.5% of the patients in the atezolizumab group and the chemotherapy group, respectively.

Pembrolizumab

Reck et al (2016) published results of the KEYNOTE-024 Trial (NCT02142738), which compared pembrolizumab to platinum-based chemotherapy in 305 patients with NSCLC and PD-L1 expression on at least 50% of tumor cells.[110,] At a median follow-up of 11.2 months, PFS was longer with pembrolizumab compared with chemotherapy (median PFS, 10.3 vs. 6 months; HR, 0.50; 95% CI, 0.37 to 0.68). The median duration of response was not reached in the pembrolizumab group and was 6.3 months in the chemotherapy group.

Nivolumab in Combination with Ipilimumab

In the CHECKMATE 227 Trial (NCT02477826) reported by Hellmann et al (2019), among the patients with a PD-L1 expression level of 1% or more, the median duration of OS was 17.1 months (95% CI, 15.0 to 20.1) with nivolumab plus ipilimumab and 14.9 months (95% CI, 12.7 to 16.7) with chemotherapy (p=.007), with 2-year OS rates of 40.0% and 32.8%, respectively.[111,] The median duration of response was 23.2 months with nivolumab plus ipilimumab and 6.2 months with chemotherapy. First-line treatment with nivolumab plus ipilimumab resulted in a longer duration of OS than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level.

Section Summary: PD-L1 Testing

In RCTs, patients with high PD-L1 expression had longer PFS and fewer adverse events when treated with anti-PD-L1 monoclonal antibodies than with platinum chemotherapy. In the KEYNOTE trial, first-line treatment with nivolumab plus ipilimumab resulted in a longer duration of OS than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level. In the EMPOWER-Lung 1 trial, first-line treatment with cemiplimab-rwlc resulted in a longer duration of OS than chemotherapy in patients with PD-L1 expression of at least 50%.

Tumor Mutational Burden Testing to Select Patients for Immunotherapy

FDA-Approved Companion Diagnostic Tissue Test

FoundationOne CDx is FDA approved as a companion diagnostic for use with pembrolizumab in patients with TMB-high (≥ 10 mutations per megabase) solid tumors.

Randomized Controlled Trial

Nivolumab plus Ipilimumab

In a subgroup analysis of the CHECKMATE 227 trial (NCT02477826), PFS was significantly longer with nivolumab plus ipilimumab (7.2 months; 95% CI, 5.5 to 13.2) than with chemotherapy (5.5 months; 95%

CI, 4.4 to 5.8) among patients with NSCLC and a high TMB (≥10 mutations per megabase).[12,]However, updated data from CHECKMATE 227 indicated that OS was improved with nivolumab plus ipilimumab regardless of TMB or PD-L1 expression levels.[111,]

Pembrolizumab

Nonrandomized Trial

Marabelle et al (2020) reported the association of high TMB with response to pembrolizumab in patients with solid tumors enrolled in a prespecified exploratory analysis of the KEYNOTE-158 study.[112,] High TMB was defined as >10 mutations per megabase according to the FoundationOne CDx panel. The proportion of patients with an objective response in the TMB-high group was 29%. At a median follow-up of approximately 3 years, the median duration of response was not reached in the TMB-high group and was 33.1 months in the non-TMB-high group. Notably, TMB-high status was associated with improved response irrespective of PD-L1. Median PFS and OS did not differ between the high and non-high TMB groups. Objective responses were observed in 24 (35%; 95% CI 24 to 48) of 68 participants who had both TMB-high status and PD-L1-positive tumors (i.e., PD-L1 combined positive score of ≥1) and in 6 (21%; 8 to 40) of 29 participants who had TMB-high status and PD-L1-negative tumors. It is unclear how generalizable these results are to patients with NSCLC, as no patients with NSCLC were enrolled in the study.

Section Summary: Tumor Mutational Burden Testing

In a subgroup analysis of an RCT, PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high TMB (≥10 mutations per megabase). However, updated data have shown that OS was improved with this regimen regardless of TMB or PD-L1 expression levels.

In a prespecified subgroup analysis of a nonrandomized trial of pembrolizumab in patients with various solid tumors, objective responses were observed in 24 (35%; 95% CI 24 to 48) of 68 participants who had both TMB-high status and PD-L1-positive tumors and in 6 (21%; 8 to 40) of 29 participants who had TMB-high status and PD-L1-negative tumors. However, this study did not enroll patients with NSCLC.

Current NCCN guidelines (v.5.2022) have removed TMB as an emerging immune biomarker for patients with NSCLC and do not recommend measurement of TMB levels to select patients for nivolumab plus ipilimumab regimens or other immune checkpoint inhibitors such as pembrolizumab.

Biomarker Testing Using Circulating Tumor DNA (Liquid Biopsy) to Select Targeted Therapy or Immunotherapy for Advanced-Stage Non-Small-Cell Lung Cancer

Selecting Targeted Therapy

Clinical Context and Test Purpose

The purpose of identifying targetable oncogenic "driver mutations" such as *EGFR* variants in patients who have NSCLC is to inform a decision whether patients should receive a targeted therapy versus another systemic therapy. Patients have traditionally been tested for driver mutations using samples from tissue biopsies.

One testing strategy is to use liquid biopsy to select first-line and second-line treatments in patients with advanced NSCLC, with reflex to tissue biopsy if the test is negative. This testing strategy is based on the reflex testing strategy suggested in the U.S. Food and Drug Administration (FDA) approval for the cobas test. Some guidelines have suggested a different testing strategy wherein testing with a liquid biopsy is considered only when testing with a tissue biopsy is not feasible.
The questions addressed in this evidence review are:

- How accurately does liquid biopsy detect driver or resistance variants of interest in the relevant patient population (clinical validity)?

- Does a strategy including liquid biopsy in patients with NSCLC improve the net health outcome compared with standard biopsy?

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with NCCN recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

The following PICO was used to select literature to inform this review.

Populations
The target population consists of patients with NSCLC where tumor biomarker testing is indicated to select a treatment. Patients may be treatment-naive, or being considered for a treatment change due to progression, recurrence, or suspected treatment resistance.

Treatment recommendations for patients with advanced NSCLC are usually made in the tertiary care setting ideally in consultation with a multidisciplinary team of pathologists, thoracic surgeons, and oncologists.

Routine surveillance or periodic monitoring of treatment response as potential uses of the liquid biopsy were not evaluated in this evidence review.

Interventions
The technology considered is an analysis of tumor biomarkers in peripheral blood (liquid biopsy) to determine treatment selection. Several commercial tests are available and many more are in development. In contrast to tissue biopsy, guidelines do not exist establishing the recommended performance characteristics of liquid biopsy.

Comparators
The relevant comparator of interest is testing for variants using tissue biopsy.

Outcomes
The outcomes of interest are OS and cancer-related survival. In the absence of direct evidence, the health outcomes of interest are observed indirectly as a consequence of the interventions taken based on the test results.

In patients who can undergo tissue biopsy, given that negative liquid biopsy results are reflexed to tissue biopsy, a negative liquid biopsy test (true or false) does not change outcomes compared with tissue biopsy.

Similarly, in patients who cannot undergo tissue biopsy, a negative liquid biopsy test (true or false) should result in the patient receiving the same treatment as he/she would have with no liquid biopsy test so a negative liquid biopsy test does not change outcomes.

The implications of positive liquid biopsy test results are described below.

Potential Beneficial Outcomes with Positive Result
For patients who can undergo tissue biopsy, the beneficial outcomes of a true-positive liquid biopsy result are the avoidance of tissue biopsy and its associated complications. In the National Lung Screening Trial, which enrolled 53454 persons at high- risk for lung cancer at 33 U.S. medical centers, the percentage of patients having at least 1 complication following a diagnostic needle biopsy was approximately 11%.[113,]

For patients who cannot undergo tissue biopsy, the beneficial outcomes of a true-positive liquid biopsy result are receipt of a matched targeted therapy instead of chemotherapy and/or immunotherapy.

Potential Harmful Outcomes with Positive Result

The harmful outcome of a false-positive liquid biopsy result is incorrect treatment with a targeted therapy instead of immunotherapy and/or chemotherapy. In a meta-analysis of RCTs of EGFR TKIs versus chemotherapy in patients without *EGFR*-sensitizing variants, the overall median progression-free survival (PFS) was 6.4 months in patients assigned to chemotherapy versus 1.9 months in patients assigned to EGFR TKIs (HR , 1.41; 95% CI , 1.10 to 1.81). The advantage of chemotherapy over EGFR TKIs for patients without *EGFR*-sensitizing variants was true in both the first- and second-line settings.[114,]

In the AZD9291 First Time In Patients Ascending Dose Study (AURA 1), single-arm, phase 1 trial of osimertinib, among 61 patients with *EGFR*-sensitizing variants who had progressed on an EGFR TKI but who did not have the *EGFR* T790M resistance variant, the response rate was 21% (95% CI, 12% to 34%) and median PFS was 2.8 months (95% CI, 2.1 to 4.3 months).[115,] There was no concurrent control group in AURA 1 for comparison of osimertinib with other second-line treatments among T790M-negative patients. However, in the IMpower 150 trial, the addition of the immunotherapy atezolizumab to the combination chemotherapy of bevacizumab, carboplatin, and paclitaxel improved PFS in a subset of 111 patients with *EGFR*-sensitizing variants or *ALK* translocations who had progressed on a prior targeted agent (median PFS, 9.7 months vs 6.1 months; HR=0.59; 95% CI 0.37 to 0.94).[116,]

Due to the poor prognosis of advanced NSCLC, the duration of follow-up for the outcomes of interest is 6 months and 1 year.

Study Selection Criteria

For the evaluation of the clinical validity of each test, studies that met the PICO criteria described above and the following eligibility criteria were considered:

- Reported on the performance characteristics (sensitivity and specificity) of the marketed version of the technology or included data sufficient to calculate sensitivity and specificity.
- Included a suitable reference standard (tissue biopsy).
- Patient/sample clinical characteristics were described and patients were diagnosed with NSCLC.
- Patient/sample selection criteria were described.
- At least 20 patients are included.

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with NCCN recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

Review of Evidence

Given the breadth of molecular diagnostic methodologies available to assess ctDNA and the lack of guidelines regarding the recommended performance characteristics of liquid biopsy,[11,] the clinical validity of each commercially available test must be established independently. Multiple high-quality studies are needed to establish the clinical validity of a test. As previously stated, extensive evidence review is not provided for FDA-approved companion diagnostic plasma tests for FDA-approved therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher. The following evidence review is organized by gene variant, and where evidence review is applicable, by test. Given the rapidly changing market, not all available tests may be represented in the

appraisal below. A current list of FDA-approved companion diagnostics is maintained at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

Testing for EGFR Variants with Circulating Tumor DNA (Liquid Biopsy)

FDA-Approved Companion Diagnostic Plasma Tests

FDA-approved companion diagnostic plasma tests to select patients for targeted therapy with kinase inhibitors on the basis of EGFR biomarkers detected via ctDNA are summarized in Table 3. For exon 19 deletion or exon 21 L858R substitution mutations, approved ctDNA tests include the cobas EGFR Mutation Test v2, Guardant360 CDx, and FoundationOne Liquid CDx tests. For detection of T790M resistance mutations to select patients for osimertinib, approved ctDNA tests include the cobas EGFR Mutation Test v2 and the Guardant360 CDx tests. For detection of EGFR exon 20 insertion mutations to select patients for amivantamab, Guardant360 CDx has received approval. These ctDNA tests are not subject to extensive evidence review. Premarket approval (PMA) details and other related studies of clinical validity are cited in Table 3 below for reference purposes only.

Table 3. FDA-Approved Companion Diagnostic Plasma Tests for *EGFR* Variants

Companion Diagnostic Plasma Test	*EGFR* Variants	PMA(s)	Related Studies of Clinical Validity
cobas EGFR Mutation Test v2	exon 19 deletion or exon 21 L858R substitution mutations for treatment selection of erlotinib, osimertinib, gefitinib, or afatinib	• P120019/S031 • P120019/S019 • P120019/S018 • P150047	• Prospective studies (Karlovich et al [2016];[117] Thress et al [2015];[118] Mok et al [2015];[119] • Retrospective studies (Jenkins et al [2017];[120] Weber et al [2014])[121]
	T790M for treatment selection of osimertinib	• P150044	
Guardant360 CDx	exon 19 deletion, exon 21 L858R substitution mutations, or T790M for treatment selection of osimertinib	• P200010	• Prospective studies (Palmero et al [2021];[122] Leighl et al [2019];[123] Thompson et al [2016])[124] • Retrospective studies (Schwaederle et al [2017];[125] Villaflor et al [2016])[126]
	exon 20 insertions for treatment selection of amivantamab	• P200010/S001	•
FoundationOneLiquid CDx	exon 19 deletion or exon 21 L858R substitution mutations for treatment selection of erlotinib, osimertinib, or gefitinib	• P190032	• Prospective studies (Schwartzberg et al [2022])[127] • Retrospective studies (Husain et al [2022])[128]

CDx: companion diagnostic; EGFR: epidermal growth factor receptor.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care.

Other *EGFR* Plasma Tests

Characteristics of clinical validity studies of liquid biopsy with tissue biopsy as the reference standard for *EGFR* variants are summarized in Table 4 for the OncoBEAM, Biodesix ddPCR, ctDx-lung, and

InVisionFirst-Lung tests. Data on the use of FoundationOne Liquid CDx to detect the actionable *EGFR* T790M variant with tissue biopsy as reference standard was not identified.[129,127,128,]

Table 4. Characteristics of Clinical Validity Studies of Liquid Biopsy With Tissue Biopsy as the Reference Standard for *EGFR* Variants

Study	Study Population	Design	Timing of Reference and Index Tests
Multiple tests			
Papadimitrakopoulou et al (2020) (AURA3)[130,]	Patients harboring T790M mutation with locally advanced or metastatic NSCLC who had progressed on EGFR TKI therapy enrolled in AURA3 studies in U.S., Mexico, Canada, Europe, Asia, and Australia	Retrospective	Both tissue and blood samples collected at screening
OncoBEAM			
Ramalingam et al (2018)[131,]	Patients with locally advanced or metastatic NSCLC from the AURA study conducted in U.S., Europe, and Asia	Prospective	Plasma was collected at baseline, time of tissue sample not specified
Karlovich et al (2016)[117,]	Patients with newly diagnosed or relapsed patients with advanced (stage IIIB, IV) NSCLC in U.S., Europe, and Australia between 2011 and 2013	Prospective	Plasma was collected within 60 d of tumor biopsy
Thress et al (2015)[118,]	Patients with NSCLC enrolled in a multinational (including U.S.) phase 1 study who had progressed on an EGFR TKI therapy	Prospective	Blood and tissue collected after progression and before next-line treatment; time between not specified
Biodesix ddPCR			
Mellert et al (2017)[132,]	Patients in the test utilization data had lung cancer; unclear whether the samples in the clinical validity data were from patients with advanced NSCLC, patient characteristics are not described	Retrospective and prospective, selection unclear	Timing not described
ctDx-Lung			
Paweletz et al (2016)[133,]	Patients in Boston with advanced NSCLC with a known tumor genotype, either untreated or progressive on therapy	Prospective	Timing not described
InVision			
Pritchet et al (2019)[134,]	Patients with untreated, advanced NSCLC; primarily from cohorts enrolled in 2 prospective US studies with 41 centers	Prospective	Blood collected within 12 weeks of tissue biopsy and no therapy between tissue and blood samples
Remon et al (2019)[135,]	Patients with advanced NSCLC enrolled in single-center, prospective observational study in France. Patients were either treatment naive for advanced disease or who had a tissue-based molecular profile that failed or was not performed on the primary tissue sample (treated rescue cohort)	Prospective	Time between tissue biopsy and blood collection less than 100 days; median time between tissue biopsy and liquid biopsy

Study	Study Population	Design	Timing of Reference and Index Tests
			collection was 34 days.

AURA3: A Phase III, Open Label, Randomized Study of AZD9291 Versus Platinum-Based Doublet Chemotherapy for Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer Whose Disease Has Progressed With Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and Whose Tumours Harbour a T790M Mutation Within the Epidermal Growth Factor Receptor Gene; ctDNA: circulating tumor DNA; EGFR: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; NSCLC: non-small-cell lung cancer; RCT: randomized controlled trial; SSED: Summary of Safety and Effectiveness Data; TKI: tyrosine kinase inhibitor.

Table 5 summarizes the results of clinical validation studies of liquid biopsy compared with tissue biopsy as a reference standard, with the exception of FoundationOne Liquid CDx, which was compared to cobas EGFR Mutation Test v2 in a non-inferiority study. Although tissue biopsy is not a perfect reference standard, the terms sensitivity and specificity will be used to describe the positive percent agreement(PPA) and negative percent agreement (NPA), respectively. For the detection of *EGFR*-resistance variants (i.e., T790M), fewer studies are available and estimates of specificity are more variable.

Table 5. Results of Clinical Validity Studies of Liquid Biopsy With Tissue Biopsy as the Reference Standard

Study	Initial N	Final N	Excluded Samples	Sensitivity (95% CI)	Specificity (95% CI)
OncoBEAM					
Ramalingam et al (2018)[131,]	60	51	Tissue or plasma not available		
***EGFR* exon 19 deletion (sensitizing)**				82 (60 to 95)	100 (88 to 100)
***EGFR* exon 21 substitution (L858R, sensitizing)**				63 (41 to 81)	96 (81 to 100)
***EGFR* exon 20 (T790M, resistance)**				100 (40 to 100)	98 (89 to 100)
Karlovich et al (2016)[117,]					
***EGFR*-sensitizing variants**	174	77	No matching tumor and plasma or inadequate tissue	82 (70 to 90)	67 (9 to 99)
***EGFR* exon 20 (T790M, resistance)**	174	77		73 (58 to 85)	50 (26 to 74)
Thress et al (2015)[118,]					
***EGFR* exon 19 deletion (sensitizing)**	NR	72	Inadequate tumor tissue	82 (63 to 94)	97 (83 to 100)
***EGFR* exon 21 substitution (L858R, sensitizing)**				87 (66 to 97)	97 (85 to 100)
***EGFR* exon 20 (T790M, resistance)**	NR	72		80 (65 to 91)	58 (36 to 78)
Biodesix ddPCR					
Papadimitrakopoulou et al (2020) (AURA3)[130,]	562		No plasma sample; mainland China patients; withdrawn informed consent; invalid tests		
***EGFR* exon 19 deletion (sensitizing)**		190		73 (64 to 80)	100 (94 to 100)
***EGFR* exon 21 substitution (L858R, sensitizing)**		189		70 (57 to 81)	98 (95 to 100)

Study	Initial N	Final N	Excluded Samples	Sensitivity (95% CI)	Specificity (95% CI)
EGFR exon 20 (T790M, resistance)		189		66 (59 to 72)	NA[d]
Mellert et al (2017)[132],					
EGFR exon 19 deletion (sensitizing)		92		96 (NR)	100 (NR)
EGFR exon 21 substitution (L858R, sensitizing)		73		100 (NR)	100 (NR)
EGFR exon 20 (T790M, resistance)		55		87 (NR)	100 (NR)
ctDx-Lung					
Paweletz et al (2016)[133],	NR	48	NR		
EGFR exon 19 deletion (sensitizing)				89 (65 to 99)[c]	100 (88 to 100)[c]
EGFR exon 21 substitution (L858R, sensitizing)				67 (9 to 99)[c]	100 (92 to 100)[c]
InVisionFirst-Lung					
Pritchet et al (2019)[134],	264		Missing tissue or ctDNA testing		
EGFR exons 18-21		114		100 (75 to 100)[b,c]	100 (96 to 100)[b,c]
Remon et al (2019)[135],	156		Missing tissue or ctDNA testing		
EGFR exons 18-21		78		88 (47 to 100)	98 (91 to 100)

CI: confidence interval; ctDNA: circulating tumor DNA; *EGFR*: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; NA: not applicable; NR: not reported; rep: replicate; SSED: Summary of Safety and Effectiveness Data.

[a] Unclear how many samples were eligible but not included

[b] Only included the subset of patients with at least 1 mutation detected by liquid biopsy

[c] Not reported; calculated based on data provided

[d] Not applicable; cannot calculate due to lack of mutation negative samples

The purpose of the limitations tables (see Tables 6 and 7) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 6. Study Relevance Limitations of Clinical Validity Studies of Liquid Biopsy With Tissue Biopsy as the Reference Standard for *EGFR* Variants

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Multiple tests					
Papadimitrakopoulou et al (2020) (AURA3)[130],					
OncoBEAM					
Ramalingam et al (2018)[131],	4. Performed in Asia				
Karlovich et al (2016)[117],					
Thress et al (2015)[118],					
Biodesix ddPCR					
Mellert et al (2017)[132],	3. Patient characteristics unclear				
ctDx-Lung					
Paweletz et al (2016)[133],	2. Unclear if same as current marketed version				
InVisionFirst-Lung					
Pritchet et al (2019)[134],	4: Calculation of performance characteristics				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
	only included subset of patients with at least 1 mutation detected by liquid biopsy				
Remon et al (2019)[135],					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 7. Study Design and Conduct Limitations of Clinical Validity Studies of Liquid Biopsy With Tissue Biopsy as the Reference Standard for *EGFR* Variants

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Multiple tests						
Papadimitrakopoulou et al (2020) (AURA3)[130],						
OncoBEAM						
Ramalingam et al (2018)[131],			1. Time between blood and tissue sample collection not described			
Karlovich et al (2016)[117],						
Thress et al (2015)[118],			1. Both samples collected after progression and before next treatment but time between blood and tissue sample collection not described			1. Precision estimates not reported but calculated based on data provided
Biodesix ddPCR						
Mellert et al (2017)[132],	1,2. Unclear how patients were selected		1. Time between blood and tissue sample collection not described			1. Precision estimates not reported cannot be calculated based on data provided
ctDx-Lung						
Paweletz et al (2016)[133],	1,2. Unclear how		1. Time between blood and tissue			1. Precision estimates not reported

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
	patients were selected		sample collection not described			but calculated based on data provided
InVisionFirst-Lung						
Pritchet et al (2019)[134,]						1. Precision estimates not reported but calculated based on data provided
Remon et al (2019)[135,]						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
FDA: U.S. Food and Drug Administration; SSED: Summary of Safety and Effectiveness Data.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Overall, the OncoBEAM test has at least 3 studies (n>200), and InVisionFirst-Lung has at least 2 studies (n>400), with the majority being of adequate quality to demonstrate the performance characteristics relative to a tissue test with tight precision estimates for *specificity* for *EGFR* TKI-sensitizing variants.

	Long time between tissue and ctDNA tests (Leighl[Leighl NB, Page RD, Raymond VM, et al. Clinical Ut.... (15): 4691-4700. PMID 30988079];Thompson[Thompson JC, Yee SS, Troxel AB, et al. Detection o.... (23): 5772-5782. PMID 27601595]; Villaflor[Villaflor V, Won B, Nagy R, et al. Biopsy-free cir.... 1): 66880-66891. PMID 27602770]); unclear patient selection (Villaflor[Villaflor V, Won B, Nagy R, et al. Biopsy-free cir.... 1): 66880-66891. PMID 27602770]); variants not stratified by type in Schwaederle[Schwaederle MC, Patel SP, Husain H, et al. Utility.... (17): 5101-5111. PMID 28539465]; very few limitations with Papadimitrakopoulou[Pap

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs comparing management with and without liquid biopsy were identified.

Evidence on the ability of liquid biopsy to predict treatment response similar to, or better than, a tissue biopsy is also of interest. If the 2 tests are highly correlated, they are likely to stratify treatment response similarly overall. To understand the implications of "false-positive" and "false-negative" liquid biopsies for outcomes, patients who have discordant results on liquid biopsy and standard biopsy are of particular interest. For example, if patients who are negative for *EGFR*-sensitizing or -resistance variants on liquid biopsies but positive for those variants on standard biopsies respond to EGFR TKIs, it would suggest that the standard biopsy was correct and the liquid biopsy results were truly false-negatives. If patients with positive liquid biopsies and negative tissue biopsies for *EGFR* variants respond to EGFR TKIs, it would suggest that the positive liquid biopsies were correct rather than false-positives.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The clinical utility might alternatively be established based on a chain of evidence. Assuming that tissue biomarkers are the standard by which treatment decisions are made, an agreement between liquid and tissue biopsies would infer that treatment selection based on liquid or tissue biopsies is likely to yield similar outcomes. Also, a liquid biopsy would reduce the number of patients undergoing tissue sampling and any accompanying morbidity.

Depending on the analytic method, compared with a tissue biopsy, liquid biopsy appears somewhat less sensitive with generally high specificity in detecting an *EGFR* TKI-sensitizing variant that can predict outcomes. This finding suggests that an *EGFR* TKI-sensitizing variant identified by liquid biopsy could be used to select a treatment with reflex to tissue biopsy. However, evidence directly demonstrating the predictive ability of liquid biopsy would be most convincing. Also, outcomes in patients who have discordant results on liquid and tissue biopsy are of particular interest.

Sufficient numbers of patients have not generally been studied in which all combinations of liquid biopsy and tissue biopsy results have been analyzed for associations with patient outcomes.[136,137,130,138,117,139,]

However, a chain of evidence, based on the sensitivity and specificity of liquid biopsy for the detection of EGFR TKI-sensitizing variants such as exon deletion 19 and L858R variants, for a test that has established clinical validity (e.g., the cobas, Guardant360 CDx, OncoBEAM, or InVision tests), can support its utility for the purpose of selecting treatment with EGFR TKIs. A robust body of evidence has demonstrated moderate sensitivity (>63%) with high specificities (>95%) for these 4 tests. If a liquid biopsy is used to detect EGFR TKI-sensitizing variants with referral (reflex) testing of tissue samples in those with negative liquid biopsies, then the sensitivity of the testing strategy will be equivalent to tissue biopsy, and the specificity will remain high between 95% and 100%. Tissue testing of biomarkers would be avoided in approximately two-thirds of patients with EGFR TKI-sensitizing variants. This strategy including tissue testing will be variably efficient depending on the prevalence of detected EGFR variants. For example, in U.S. populations with an assumed prevalence of EGFR TKI-sensitizing variants of 15% and a 75% sensitive and 97% specific liquid biopsy test (e.g., cobas), 86% of the patients would then require tissue testing to detect the remaining patients with variants; 3% would receive targeted therapy after liquid biopsy who would have received a different systemic

therapy if tested with tissue biopsy; and 11% would appropriately receive targeted therapy following liquid biopsy without having to undergo tissue biopsy. In other populations such as Asians where the prevalence of EGFR TKI-sensitizing variants is 30% to 50%, the strategy would be more efficient, and a lower proportion of patients would be subject to repeat testing. There is extremely limited evidence on whether the "false-positives" (i.e., patients with positive liquid biopsy and negative tissue biopsy) might have been incorrectly identified as negative on tissue biopsy. In 1 study, 3 patients with negative tissue biopsies and positive liquid biopsies appeared to respond to EGFR TKI inhibitors.

The diagnostic characteristics of liquid biopsy for the detection of T790M variants associated with EGFR TKI-inhibitor resistance, an indication for treatment with osimertinib, has shown that liquid biopsy is moderately sensitive and moderately specific and thus overall concordance is moderate. Using tissue testing of negative liquid biopsies would increase sensitivity, but because liquid biopsy is not highly specific, it would result in false-positives. Because not enough data are available to determine whether these false-positives represent a faulty tissue reference standard or are correctly labeled as false-positives, outcomes for these patients are uncertain. In 1 study, 8 patients with negative tissue biopsies but positive liquid biopsies had low response rates consistent with those with negative tissue biopsies; and in the AURA study, 18 patients with liquid-positive, tissue-negative results had a low response rate, also consistent with negative tissue biopsy.[130,] In the TIGER-X study, 3 patients who were liquid-positive, tissue-negative had low response rates to rociletinib, similar to the other tissue-negative patients.[139,] However, although there is higher discordance in the liquid versus tissue results for the resistance variant, retrospective analyses have suggested that patients positive for T790M in liquid biopsy have outcomes with osimertinib that appear to be similar overall to patients positive by a tissue-based assay. In the AURA3 trial, T790M tissue-positive patients treated with osimertinib who were liquid-negative had longer median PFS compared to liquid-positive patients, a trend that may be associated with increased plasma test sensitivity in individuals with advanced disease.[130,]

Section Summary: Testing for *EGFR* Variants with Circulating Tumor DNA (Liquid Biopsy)
Several plasma tests have received FDA-approval as companion diagnostics for selection of therapies on the basis of *EGFR* biomarkers detected via ctDNA. In additional to plasma tests with FDA-approved companion diagnostic status, the Oncobeam and InVision tests have established sufficient sensitivity and specificity for detection of *EGFR* TKI-sensitizing variants using tissue biopsy as reference standard when reflex testing to tissue is employed for plasma-negative tests.

Few studies have examined the performance of liquid biopsy for the detection of T790M variants associated with *EGFR* TKI resistance and several different tests were used in the studies. Detection of these variants is potentially important for liquid biopsy because this variant is of interest after the initiation of treatment, when biopsies may be more difficult to obtain. Unlike the high specificities compared with tissue biopsy demonstrated for *EGFR* variants associated with TKI sensitivity, the moderate specificity means that liquid biopsy often detects T790M variants when they are not detected in tissue biopsy. Sacher et al (2016) suggested that these false-positives might represent tumor heterogeneity in the setting of treatment resistance, such that the T790M status of the biopsied site might not represent all tumors in the patient.[140,]

Testing for ALK Rearrangements with Circulating Tumor DNA (Liquid Biopsy)

FDA-Approved Companion Diagnostic Plasma Tests

In October 2020, FoundationOne Liquid CDx received FDA-approval as a companion diagnostic to select patients for treatment with alectinib. Approval was based on a clinical bridging study using pre-treatment plasma samples from Cohort A of the Blood First Assay Screening Trial (BFAST) which yielded a PPA of 84.05 (95% CI, 73.7% to 91.4%) and NPA of 100% (95% CI, 97.9% to 100.05%) for samples with at least 30 ng of DNA.[141,] The median ORR was 88.9% (95% CI, 78.4% to 95.4%) for the liquid-positive population which was comparable with the observed ORR for the *ALK*-positive population as determined via clinical trial assay (87.4%; 95% CI, 78.5% to 93.5%).[142,] Similar results

were seen in samples with at least 20 ng of DNA. Reflex testing of plasma negative samples is recommended due to responses seen in plasma-negative and tissue-positive patients in the ALEX trial of alectinib versus crizotinib.[141,]

Section Summary: Testing for *ALK* Rearrangements with Circulating Tumor DNA (Liquid Biopsy)

One liquid biopsy test, FoundationOne Liquid CDx, has received FDA approval as a companion diagnostic to select patients for treatment with alectinib based on the presence of *ALK* rearrangements as detected via ctDNA.

Testing for MET Exon 14 Skipping Alterations with Circulating Tumor DNA (Liquid Biopsy)

FDA-Approved Companion Diagnostic Plasma Tests

In July 2021, FoundationOne Liquid CDx received FDA approval as a companion diagnostic to select patients for treatment with capmatinib. Approval was based on a clinical bridging study using pre-treatment plasma samples and clinical outcome data from patients with NSCLC enrolled in the GEOMETRY mono-1 trial, an open-label, single arm, phase 2 trial of targeted treatment with capmatinib.[106,] The clinical bridging study is described in the SSED associated with FDA approval of FoundationOne Liquid as a companion diagnostic test for capmatinib.[143,] The SSED notes that based on the low PPA between the plasma test and the clinical trial assay (70.5%; 95% CI 59.1% to 80.3%), a reflex testing using tissue specimens to an FDA approved tissue test will be required, if feasible, if the plasma test is negative. The corresponding NPA was 100% (95% CI, 95.9% to 100%). Overall response rates for liquid- and tissue-positive patients were 48.8% (95% CI, 32.9% to 64.9%) and 81.3% (95% CI, 54.4% to 96.0%) for Cohorts 4 and 5b with minimum DNA sample requirements of 20 ng.

Section Summary: Testing for *MET* Exon 14 Skipping Alterations with Circulating Tumor DNA (Liquid Biopsy)

One liquid biopsy test, FoundationOne Liquid CDx, has received FDA approval as a companion diagnostic to select patients for treatment with capmatinib based on the presence of *MET* exon 14 skipping alterations as detected via ctDNA, on the basis of a clinical bridging study.

Testing for KRAS Variants with Circulating Tumor DNA (Liquid Biopsy)

FDA-Approved Companion Diagnostic Plasma Tests

In May 2021, Guardant360 CDx received FDA approval as a companion diagnostic test to select patients for treatment with sotorasib based on the presence of *KRAS* G12C mutated NSCLC. Approval was based on a clinical bridging study using pre-treatment plasma samples and clinical outcome data from patients with NSCLC enrolled in the phase 1/2 multicenter, nonrandomized, open-label Amgen 20170543 clinical study which supported the FDA approval of sotorasib.[144,] The PPA and NPA with respect to the therascreen KRAS RGQ PCR Kit tissue test was 71.6% (95% CI, 62.1% to 79.8%) and 100% (95% CI, 95.0% to 100%), respectively. The ORR for Guardant360 CDx was 38% (95% CI, 27% to 49%) compared to 36% (95% CI, 28% to 45%) in the full analysis population. Duration of response was 7.1 months (95% CI, 1.3 to 8.4) for Guardant360 CDx compared to 10.0 months (95% CI, 1.3 to 11.1) in the full analysis population.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Other *KRAS* Plasma Tests

The clinical validity of the FoundationOne Liquid CDx test for detecting *KRAS* variants has been evaluated in several published studies of patients with NSCLC. Study characteristics and results are shown in Tables 8 and 9. Study relevance, design, and conduct limitations are described in Tables 10 and 11.

Table 8. Characteristics of Clinical Validity Studies of Liquid Biopsy for *KRAS* Variants

Study	Study Population	Design	Reference Standard	Timing of Tissue Biopsy and Liquid Biopsy	Blinding of Assessors
FoundationOne Liquid CDx					
Husain et al (2022)[128,]	• Liquid biopsies ordered within the United States between September 2020 to October 2021 during routine clinical care, including 613 patients with NSCLC with available tissue results	Retrospective	CGP of tissue samples via NGS (Foundation One CDx)	Plasma collection for liquid CGP was within a median time of 304 days (IQR: 27 to 670 days) after tissue collection.	Not described
Schwartzberg et al (2022)[127,]	• Patients with metastatic, nonsquamous NSCLC enrolled in the Prospective Clinicogenomic Program clinical trial (NCT04180176) through June 2021 • CGP testing of both tissue and plasma was available for 131 patients; CGP testing of plasma with tissue testing of up to 5 genes was available for 264 patients; CGP testing of plasma with no available tissue testing was applicable for 120 patients	Prospective	Optional CGP of tissue samples via NGS (Foundation One CDx); Tissue assay used for testing of up to 5 genes not specified.	Pre-treatment plasma and tissue samples used for analysis. Both FoundationOne Liquid and FoundationOne Liquid CDx tests used.	Not described

CDx: companion diagnostic; CGP: comprehensive genomic profiling; IQR: interquartile range; *KRAS*: Kirsten rat sarcoma virus; NGS: next-generation sequencing; NSCLC: non-small-cell lung cancer.

Table 9. Results of Clinical Validity Studies of Liquid Biopsy for *KRAS* Variants

Study	Initial N	Final N	Excluded Samples	*KRAS* Variant-Positive, %[a]	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
FoundationOne Liquid CDx								
Husain et al (2022)[128,]	613	613	None; only tissue-matched samples were evaluated	22.8	68.5 (60.1 to 76.0)[b]	98.7 (97.1 to 99.5)[b]	94.1 (87.1 to 97.6)[b]	91.4 (88.5 to 93.6)[b]
		128	Excluded samples without elevated tumor shed (i.e., tumor fraction <10%)	12.5	93.8 (67.7 to 99.7)[b]	98.2 (93.1 to 99.7)[b]	88.2 (62.3 to 97.9)[b]	99.1 (94.4 to 100)[b]
Schwartzberg et al (2022)[127,]	768	304	No liquid biopsy or tissue biopsy available or presence of squamous tumor histology	41.4	72.2 (63.4 to 79.6)[b]	97.8 (94.0 to 99.3)[b]	95.8 (89.0 to 98.6)[b]	83.3 (77.3 to 87.9)[b]

Study	Initial N	Final N	Excluded Samples	*KRAS* Variant-Positive, %[a]	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
		68	Excluded samples without elevated tumor shed (i.e., tumor fraction <10%)	28.0	100 (80.8 to 100)[b]	96.3 (86.2 to 99.4)[b]	91.3 (70.5 to 98.5)[b]	100 (91.4 to 100)[b]

CI: confidence interval; *KRAS*: Kirsten rat sarcoma virus; NPV: negative predictive value; PPV: positive predictive value.
[a] With tissue biopsy reference standard.
[b] Calculated from reported data.

Table 10. Clinical Validity Study Relevance Limitations for Liquid Biopsy of *KRAS* Variants

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
FoundationOne Liquid CDx					
Husain et al (2022)[128,]	3. NSCLC study population was not described	1. Unclear what tumor fraction thresholds are used and/or reported in the currently marketed test; 3. Unclear whether actionable *KRAS* G12C variant was detected	2. Reference standard was FoundationOne CDx tissue assay		
Schwartzberg et al (2022)[127,]	4. Most patients were previously untreated, which is not the population of interest for treatment with sotorasib	1. Unclear what tumor fraction thresholds are used and/or reported in the currently marketed test; 3. Two different versions of the liquid biopsy test were used	2. Reference standard was FoundationOne CDx tissue assay; unclear which tissue assay was used for patients receiving non-CGP testing for up to 5 genes	3. Complete concordance data for actionable *KRAS* G12C variant was not provided	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
NSCLC: non-small-cell lung cancer.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not

explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 11. Clinical Validity Study Design and Conduct Limitations for Liquid Biopsy of *KRAS* Variants

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
FoundationOne Liquid CDx						
Husain et al (2022)[128,]	1. Not clear whether concordance samples were consecutive or convenience or how they were selected from those eligible.	1. Blinding not described	2. Timing of liquid and tissue biopsy varied (median, 304 days) and was not specified for NSCLC subgroup	1. Not registered	1. Only participants with available tissue and plasma results were included	
Schwartzberg et al (2022)[127,]	1. Not clear whether concordance samples were consecutive or convenience	1. Blinding not described	1. Timing of tests not described		3. Large proportion of missing tissue biopsy data	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Follow-Up key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples/patients excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified on the clinical utility of liquid biopsy for detection of actionable *KRAS* variants with the FoundationOne Liquid CDx to guide treatment for patients with NSCLC.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Testing for *KRAS* Variants with Circulating Tumor DNA (Liquid Biopsy)
One liquid biopsy test, Guardant360 CDx, has received FDA approval as a companion diagnostic to select patients with *KRAS* G12C-mutated NSCLC for treatment with sotorasib.

The clinical validity of the FoundationOne Liquid CDx test has been studied in 1 retrospective and 1 prospective study. When compared to tissue biopsy, sensitivity ranged from 68.5% to 72.2% for tumor fractions <10% and from 93.8% to 100% for tumor fractions ≥10%. Specificity was consistently >96% across studies and tumor shed thresholds. Major clinical validity study limitations included unclear relevance to the intended use population and the currently marketed test versions and limited reporting of performance characteristics for the actionable *KRAS* G12C variant. No published studies reporting on corresponding clinical outcomes were identified.

Testing for ROS1 Rearrangements with Circulating Tumor DNA (Liquid Biopsy)

FDA-Approved Companion Diagnostic Plasma Tests

No plasma tests have received FDA approval as companion diagnostics to select patients with *ROS1* rearrangements for treatment with crizotinib or entrectinib. The FoundationOne CDx and Oncomine DX Target Test tissue assays were previously approved to select patients with *ROS1* fusions for treatment with entrectinib and crizotinib, respectively.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Other *ROS1* Plasma Tests

The clinical validity of the FoundationOne Liquid CDx test for detecting *ROS1* fusions has been evaluated in pre-treatment samples of patients with NSCLC. Study characteristics and results are shown in Tables 12 and 13. Study relevance, design, and conduct limitations are described in Tables 14 and 15.

Table 12. Characteristics of Clinical Validity Studies of Liquid Biopsy for *ROS1* Rearrangements

Study	Study Population	Design	Reference Standard	Timing of Tissue Biopsy and Liquid Biopsy	Blinding of Assessors
FoundationOne Liquid CDx					
Dziadziuszko et al (2022)[145,]	• Patients with locally advanced ormetastatic *ROS1* or *NTRK* fusion-positive NSCLC who had received no prior TKI therapy and were enrolled through May 2018 in the phase 2, multicenter, multinational STARTRK-2 trial (NCT02568267) designed to evaluate the efficacy of entrectinib	Retrospective	For the *ROS1* cohort, one central and 11 local testing laboratories were used to enroll study participants using the following technologies: FISH (n=15); RNA-NGS (n=27); and DNA-NGS (n=9). The central testing clinical trial assay was the Trailblaze Pharos assay. If patients were enrolled by local testing laboratories and a tumor sample was available,	Liquid biopsy was performed on frozen, pre-treatment plasma samples.	Primary endpoints were assessed by blinded independent central review.

Study	Study Population	Design	Reference Standard	Timing of Tissue Biopsy and Liquid Biopsy	Blinding of Assessors
			independent central molecular NGS testing with the Trailblaze Pharos assay was performed.		

CDx: companion diagnostic; DNA: deoxyribonucleic acid; FISH: fluorescence in situ hybridization; NGS: next-generation sequencing; NSCLC: non-small-cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; RNA: ribonucleic acid; ROS1: c-ros oncogene 1; STARTRK-2: Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions); TKI: tyrosine kinase inhibitor.

Table 13. Results of Clinical Validity Studies of Liquid Biopsy for *ROS1* Rearrangements

Study	Initial N	Final N	Excluded Samples	*ROS1* Fusion-Positive, %[a]	PPA, % (95% CI)	NPA, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
FoundationOne Liquid CDx								
Dziadziuszko et al (2022)[145,]	86	31	Samples not evaluable via liquid biopsy and those with DNA content <30 ng were excluded; only *ROS1* tissue-positive samples were evaluated in clinical bridging study	100;[b] 1-2[c]	64.5 (45.4 to 80.8)	100 (93.4 to 100)	100 (83.9 to 100)	99.6 (99.4 to 99.8)

CDx: companion diagnostic; CI: confidence interval; DNA: deoxyribonucleic acid; NPA: negative percent agreement; NPV: negative predictive value; PPA: positive percent agreement; PPV: positive predictive value; ROS1: c-ros oncogene 1.
[a] With tissue biopsy reference standard.
[b] Clinical bridging study only evaluated *ROS1* fusion-positive samples as determined by clinical trial assay.
[c] Previously published *ROS1* fusion prevalence rate was used to estimate PPV and NPV.

Table 14. Study Relevance Limitations for Liquid Biopsy of *ROS1* Rearrangements

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
FoundationOne Liquid CDx					
Dziadziuszko et al (2022)[145,]	3. NSCLC study population for clinical bridging study was not described		2-3. Several clinical trial assays with varying detection methodologies (FISH, DNA-NGS, RNA-NGS) were used	3. Clinical bridging study is not able to provide full concordance data as only tissue-positive patients were evaluated; potential liquid false-positives cannot be evaluated	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CDx: companion diagnostic; DNA: deoxyribonucleic acid; FISH: fluorescence in situ hybridization; NGS: next-generation sequencing; NSCLC: non-small-cell lung cancer; ROS1: c-ros oncogene 1; RNA: ribonucleic acid.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear;

4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 15. Study Design and Conduct Limitations for Liquid Biopsy of ROS1 Rearrangements

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
FoundationOne Liquid CDx						
Dziadziuszko et al (2022)[145,]	1. Selection not described	1. Primary endpoints were assessed by blinded independent central review; only tissue-positive patients were evaluated	1. Pre-treatment plasma specimens were used but timing of tests was not described		3. No data on potential liquid false-positives is available	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Follow-Up key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples/patients excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified on the clinical utility of liquid biopsy with FoundationOne Liquid CDx for detection of *ROS1* rearrangements to guide treatment with entrectinib for patients with NSCLC.

Chain of Evidence

Dziadziuszko et al (2022) published entrectinib clinical efficacy outcomes based on FoundationOne Liquid CDx results and clinical trial assay (CTA) results for *ROS1* fusions.[145,] For liquid-positive patients (n=18), the ORR was 72.2% (95% CI, 46.5% to 90.3%) compared to 72.7% (95% CI, 39.0 to 94.0) in liquid-negative patients (n=11), respectively (p=1.00). Corresponding median duration of response was significantly longer in the liquid-negative group (p=.009) at 17.3 months (interquartile range [IQR], 13.9 to 18.8) compared to 5.6 months (IQR, 3.5 to 11.4) in the liquid-positive group. The investigators hypothesize that *ROS1* fusion detection via FoundationOne Liquid CDx could act as a prognostic test

for poorer patient outcomes, as the likelihood of detecting gene fusions may be higher in samples from patients with higher tumor burden and enhanced tumor shedding. No data on tissue-negative patients was available to evaluate potential liquid false-positives.

However, indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Testing for *ROS1* Rearrangements with Circulating Tumor DNA (Liquid Biopsy)
No liquid biopsy tests have received FDA approval as companion diagnostics to select patients with ROS1 fusion-positive NSCLC for treatment with crizotinib or entrectinib.

The clinical validity of the FoundationOne Liquid CDx test has been evaluated in a retrospective clinical bridging study. Compared to clinical trial assays, PPA and NPA were 64.5% (95% CI, 45.4% to 80.8%) and 100% (95% CI, 93.4% to 100%), respectively. However, interpretation is limited as clinical trial assays did not use a standardized detection method and study sample size was small. Corresponding ORRs were 72.2% in liquid-positive patients compared to 72.7% in liquid-negative patients. Median duration of response was significantly shorter in liquid-positive patients (5.6 vs. 17.3 months), potentially relating to higher tumor burden and enhanced tumor shedding. These data need to be confirmed in additional, well-designed studies. No data on tissue-negative patients was available to evaluate potential liquid false-positives.

Testing for HER2 Variants with Circulating Tumor DNA (Liquid Biopsy)

FDA-Approved Companion Diagnostic Plasma Tests
In August 2022, Guardant360 CDx received FDA approval as a companion diagnostic test to select NSCLC patients with *HER2* activating mutations for treatment with fam-trastuzumab deruxtecan-nxki (Enhertu). Approval was based on a clinical bridging study that included 89 patients from Cohort 2 of the DESTINY-Lung 01 trial and 111 subjects from a sensitivity analysis prevalence set.[146,] Overall PPA and NPA were 91.1% (95% CI, 83.2% to 96.1%) and 100.0% (95% CI, 96.7% to 100.0%), respectively. The ORR for the Guardant360 CDx clinical efficacy population was 58.0% (95% CI, 46.5% to 68.9%) with a median duration of response (DOR) of 9.25 months (95% CI, 5.7 to 18.2) which was comparable to results observed in the DESTINY-Lung 01 (ORR, 54.9%; mDOR, 9.3 months) and DESTINY-Lung 02 trials (ORR, 57.7%; mDOR, 8.7 months).

Section Summary: Testing for *HER2* Variants with Circulating Tumor DNA (Liquid Biopsy)
One liquid biopsy test, Guardant360 CDx, has received FDA approval as a companion diagnostic to select patients with NSCLC and *HER2* activating mutations for treatment with trastuzumab deruxtecan.

Summary of Evidence
For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive somatic testing for *EGFR* variants and *ALK* rearrangements, the evidence includes nonrandomized studies and phase 3 studies comparing tyrosine kinase inhibitors (TKIs) (e.g., afatinib, erlotinib, gefitinib, osimertinib, dacomitinib, et al) with chemotherapy or alternate TKIs. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, quality of life (QOL), and treatment-related morbidity. Studies have shown that TKIs are superior to chemotherapy regarding tumor response rate and progression-free survival (PFS), with a reduction in toxicity and improvement in QOL. Recent data has also shown that patients with *EGFR* exon 20 insertion mutations may benefit from immunotherapy with amivantamab-vmjw following disease progression on platinum-based chemotherapy or ramucirumab in combination with erlotinib as first-line treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive somatic testing for *BRAF* variants and *ROS1* rearrangements, the evidence includes nonrandomized trials and observational studies of BRAF and MEK inhibitors and crizotinib or ceritinib, respectively. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown that combination therapy with dabrafenib and trametinib for *BRAF* V600E- variant NSCLC and crizotinib for NSCLC with *ROS1* rearrangements result in response rates of 60% and 70%, respectively, with acceptable toxicity profiles. In an analysis of 53 patients with *ROS-1* fusion -positive NSCLC enrolled in 3 ongoing clinical trials of entrectinib, the objective response rate was 77%, with a median duration of response of 24.6 months and acceptable toxicity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive somatic testing for *RET* or *MET* gene testing, the evidence includes nonrandomized trials of kinase inhibitors. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown efficacy in PFS and duration of response for selpercatinib and pralsetinib in patients with RET-fusion positive NSCLC, and for capmatinib in patients with *MET* Exon 14 skipping alterations, with acceptable toxicity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive somatic testing for *KRAS* as a technique to predict treatment nonresponse to anti-EGFR therapy with TKIs or testing for *HER2* variants to select the use of the anti-EGFR monoclonal antibody cetuximab (Erbitux), the evidence includes post hoc analysis of trials, observational studies, and meta-analyses. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Data on the role of *KRAS* variants in NSCLC and response to erlotinib are available from post hoc analysis of trials, observational studies, and meta-analyses. Although studies have shown that *KRAS* variants in patients with NSCLC confer a high level of resistance to TKIs, data are insufficient to assess any additional benefit to *KRAS* testing beyond *EGFR* testing. In 2 randomized trials with post hoc analyses of *KRAS* variant status and use of the anti-EGFR monoclonal antibody cetuximab with chemotherapy, *KRAS* variants did not identify patients who would benefit from anti-EGFR antibodies, because outcomes with cetuximab were similar regardless of *KRAS* variant status, Studies for *HER2* variant testing have reported response rates and PFS in numbers of patients too small from which to draw conclusions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who receive somatic testing for *KRAS* variants to select targeted treatment, the evidence includes a phase 2, open-label trial of sotorasib in patients with *KRAS* variant NSCLC. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Presence of the KRAS alteration in tissue was confirmed on central laboratory testing with the use of the therascreen KRAS RGQ PCR Kit. Among 124 patients evaluated for the primary outcome, 4 (3.2%) had a complete response and 42 (33.9%) had a partial response, with an acceptable safety profile. Median duration of response was 11.1 months (95% confidence interval [CI]: 6.9 to not evaluable). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy with fam-trastuzumab deruxtecan-nxki who receive somatic testing for *HER2* variants, the evidence includes a multicenter, blinded, and randomized dose-optimization trial. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In the DESTINY-Lung02 trial, patients with activating *HER2* mutations who have received prior systemic therapy demonstrated an ORR of 58% (95% CI, 43% to 71%) and median duration of response of 8.7 months (95% CI, 7.1 months to not estimable) when treated with the novel antibody-drug conjugate

trastuzumab deruxtecan. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.
For individuals who have advanced-stage NSCLC who are being considered for immunotherapy who receive PD-L1 testing, the evidence includes randomized controlled trials (RCTs) comparing immunotherapy to chemotherapy. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In RCTs, patients with high PD-L1 expression had longer PFS and fewer adverse events when treated with anti-PD-L1 monoclonal antibodies than with platinum chemotherapy. In the KEYNOTE trial, first-line treatment with nivolumab plus ipilimumab resulted in a longer duration of OS than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy who receive tumor mutational burden (TMB) testing, the evidence includes a RCT and retrospective observational studies. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In a subgroup analysis of the KEYNOTE trial, PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high TMB ($\geq$10 mutations per megabase). In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and OS in patients receiving immunotherapy. These results need to be confirmed in additional, well-designed prospective studies. Additionally, there is no consensus on how to measure TMB and current NCCN guidelines no longer recognize it as an emerging biomarker for NSCLC. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who receive testing for biomarkers of EGFR TKIs sensitivity using ctDNA with the cobas EGFR Mutation Test v2, Guardant360 CDx, FoundationOne Liquid CDx, OncoBEAM, or InVision tests, the evidence includes numerous studies assessing the diagnostic characteristics of liquid biopsy compared with tissue biopsy. Relevant outcomes are OS, disease-specific survival, and test validity. Current evidence does not permit determining whether cobas or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA identified no RCTs providing evidence of the clinical utility of cobas. The cobas, Guardant360 CDx, and FoundationOne Liquid CDx tests have received FDA-approval as companion diagnostics for EGFR-sensitizing variants and are therefore not subject to extensive evidence review. The OncoBEAM and InVision tests have adequate evidence of clinical validity for the EGFR TKI-sensitizing variants. A chain of evidence demonstrates that the reflex testing strategy with these tests should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds of patients with EGFR TKI-sensitizing variants. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. These tests can identify patients for whom there is a net benefit of targeted therapy versus chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who receive testing for biomarkers of *EGFR* TKIs sensitivity using ctDNA (liquid biopsy) with tests other than the cobas EGFR Mutation Test v2, Guardant360 CDx, FoundationOne Liquid CDx, OncoBEAM or InVision tests, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with reference standard. Relevant outcomes are OS, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the other commercially available tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision. Current evidence does not permit determining whether a liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA found no RCTs providing evidence of the clinical utility of these methods of liquid biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who progressed on *EGFR* TKIs who receive testing for biomarkers of *EGFR* TKI resistance using ctDNA (liquid biopsy) with the cobas EGFR Mutation Test v2, Guardant360 CDx, OncoBEAM, or InVision tests the evidence includes studies assessing the diagnostic characteristics of liquid biopsy. Relevant outcomes are OS, disease-specific survival, and test validity. Both cobas and Guardant360 CDx tests have been FDA-approved as companion diagnostic plasma tests for selection of osimertinib treatment in patients with T790M-mutated NSCLC on the basis of clinical bridging studies and are therefore not subject to extensive evidence review. Given the moderate clinical sensitivity and specificity of liquid biopsy for the remaining tests, using liquid biopsy alone or in combination with tissue biopsy might result in the selection of different patients testing positive for *EGFR* TKI resistance. It cannot be determined whether patient outcomes are improved. Although there is higher discordance in the liquid versus tissue results for the resistance variant, retrospective analyses have suggested that patients positive for T790M in liquid biopsy have outcomes with osimertinib that appear to be similar overall to patients positive by a tissue-based assay. Additionally, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published joint guidelines endorsed by American Society of Clinical Oncology with an expert consensus opinion that physicians may use liquid biopsy (cell-free DNA) to identify *EGFR* T790M variants in patients with progression or resistance to *EGFR*-targeted TKIs and that testing of the tumor sample is recommended if the liquid biopsy result is negative. Similarly, the National Comprehensive Cancer Network guidelines also state that at progression on erlotinib, afatinib, gefitinib or dacomitinib when testing for the T790M resistance variant, liquid biopsy should be considered. When a liquid biopsy is negative, tissue-based testing is strongly recommended. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who progressed on *EGFR* TKIs who receive testing for biomarkers of *EGFR* TKI resistance using ctDNA (liquid biopsy) with tests other than the cobas EGFR Mutation Test v2, Guardant360 CDx, OncoBEAM, or InVision tests, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy. Relevant outcomes are OS, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the other commercially available tests have multiple studies of adequate quality to estimate the performance characteristics for detection of the *EGFR* T790M variant with sufficient precision. Current evidence does not permit determining whether a liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA found no RCTs providing evidence of the clinical utility of these methods of liquid biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with advanced-stage NSCLC who are being considered for targeted therapy who undergo testing for *ALK* rearrangements or *MET* exon 14 skipping alterations using FoundationOne Liquid CDx, the evidence includes clinical bridging studies. Relevant outcomes are OS, disease-specific survival, and test validity. FoundationOne Liquid CDx has received FDA-approval as a companion diagnostic plasma test for alectinib and capmatinib and is therefore not subject to extensive evidence review. FDA approval was based on sufficient sensitivity against clinical trial assays as reference standard to support a reflex testing strategy and favorable overall response rates in the liquid-positive subpopulation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with advanced-stage NSCLC who are being considered for targeted therapy who undergo testing for *KRAS* variants or *ROS1* rearrangements using FoundationOne Liquid CDx, the evidence includes several retrospective and prospective studies assessing the diagnostic characteristics of liquid biopsy compared with tissue reference standard. Relevant outcomes are OS, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies

available to assess ctDNA, the clinical validity of each commercially available test must be established independently. Studies have had small sample sizes and have failed to focus on the actionable *KRAS* G12C variant. Multiple studies of adequate quality to estimate the performance characteristics with sufficient precision are lacking. Current evidence does not permit determining whether a liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA found no RCTs providing evidence of the clinical utility of this method of liquid biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with advanced-stage NSCLC who are being considered for targeted therapy or immunotherapy who undergo testing for *KRAS* or *HER2* variants using Guardant360 CDx, the evidence includes clinical bridging studies. Relevant outcomes are OS, disease-specific survival, and test validity. Guardant360 CDx received FDA-approval as a companion diagnostic plasma test for sotorasib and fam-trastuzumab deruxtecan-nxki and is therefore not subject to extensive evidence review. FDA approval was based on sufficient sensitivity against clinical trial assays as reference standard to support a reflex testing strategy and favorable overall response rates in the liquid-positive subpopulation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Chest Physicians Guidelines

In 2013, the American College of Chest Physicians updated its evidence-based practice guidelines on the treatment of stage IV non-small-cell lung cancer (NSCLC).[147,] Based on a review of the literature, the College reported improved response rates, progression-free survival, and toxicity profiles with first-line erlotinib or gefitinib compared with first-line platinum-based therapy in patients with *EGFR* variants, especially exon 19 deletion and L858R. The College recommended, "testing patients with NSCLC for *EGFR* mutations at the time of diagnosis whenever feasible, and treating with first-line EGFR TKIs if mutation-positive."

American Society of Clinical Oncology

In 2021, the American Society of Clinical Oncology (ASCO) and Ontario Health published updated guidelines on therapy for stage IV NSCLC with driver alterations. [148,] The updated recommendations were based on a systematic review of randomized controlled trials from December 2015 to January 2020 and meeting abstracts from ASCO 2020. The recommendations include the following:

- All patients with nonsquamous NSCLC should have the results of testing for potentially targetable mutations (alterations) before implementing therapy for advanced lung cancer, regardless of smoking status, when possible.
- Targeted therapies against ROS1 fusions, BRAF V600E mutations, RET fusions, MET exon 14 skipping mutations, and NTRK fusions should be offered to patients, either as initial or second-line therapy when not given in the first-line setting.
- Chemotherapy is still an option at most stages.

In 2022, the ASCO published a guideline on the management of stage III NSCLC.[149,] The recommendations were based on a literature search of systematic reviews, meta-analyses, and randomized controlled trials published from 1990 through 2021. Relevant recommendations include the following:

- Presence of oncogenic driver alterations, available therapies, and patient characteristics should be taken into account.
- Patients with resected stage III NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutation may be offered adjuvant osimertinib after platinum-based chemotherapy.

College of American Pathologists et al

In 2013, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published evidence-based guidelines for molecular testing to select patients with lung cancer for treatment with EGFR and ALK TKI therapy.[150,] Based on excellent quality evidence (category A), the guidelines recommended *EGFR* variant and *ALK* rearrangement testing in patients with lung adenocarcinoma regardless of clinical characteristics (e.g., smoking history).

In 2018, updated guidelines were published and added new *EGFR* and *ALK* recommendations.[151,] *ROS1* testing is recommended for all patients with lung adenocarcinoma irrespective of clinical characteristics (strong recommendation). *BRAF*, *RET*, *HER2*, *KRAS*, and *MET* testing are not recommended as routine stand-alone tests, but may be considered as part of a larger testing panel or if *EGFR*, *ALK*, and *ROS1* are negative (expert consensus opinion).

National Comprehensive Cancer Network Guidelines

Testing for Molecular Biomarkers

NCCN guidelines on NSCLC (v.5.2022) provide recommendations for individual biomarkers that should be tested, and recommend testing techniques. Guidelines are updated frequently; refer to the source document for current recommendations. The most recent guidelines (v.5.2022) include the following recommendations and statements related to testing for molecular biomarkers:[11,]

- Broad molecular profiling systems may be used to simultaneously test for multiple biomarkers.
- To minimize tissue use and potential wastage, the NCCN NSCLC Panel recommends that broad molecular profiling be done as part of biomarker testing using a validated test(s) that assesses potential genetic variants:
  - *ALK* rearrangements
  - *EGFR* mutations
  - *BRAF* mutations
  - *MET* exon 14 skipping mutations
  - *RET* rearrangements
  - *ERBB2* (*HER2*) mutations
  - *KRAS* mutations
  - *NTRK* 1/2/3 gene fusions
  - *ROS1* rearrangements
- Both FDA and laboratory-developed test platforms are available that address the need to evaluate these and other analytes.
- Broad molecular profiling is also recommended to identify emerging biomarkers for which effective therapy may be available, such as high-level *MET* amplifications.
- Clinicopathologic features should not be used to select patients for testing.
- The guidelines do not endorse any specific commercially available biomarker assays or commercial laboratories.

Plasma Cell-Free/Circulating Tumor DNA Testing:

The NCCN guidelines on NSCLC (v.5.2022 include the following recommendations related to plasma cell-free/circulating tumor DNA testing.[11,]

- Plasma cell free/circulating tumor DNA testing should not be used to diagnose NSCLC; tissue should be used to diagnose NSCLC.
- Plasma cell free/circulating tumor DNA testing should not be used in lieu of a histologic tissue diagnosis, but cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, notably:
  - If the patient is medically unfit for invasive tissue sampling; or
  - In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA should be used only if follow-up tissue-based analysis is planned for all patients in which an oncogenic driver is not identified.
  - In the initial diagnostic setting, if tissue-based testing does not completely assess all recommended biomarkers owing to tissue quantity or testing methodologies available, consider repeat biopsy and/or cell-free/circulating tumor DNA testing.

The guidelines also state:

- Standards for analytic performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare and Medicaid Services will cover diagnostic testing with next-generation sequencing for beneficiaries with recurrent, relapsed, refractory, metastatic cancer, or advanced stages III or IV cancer if the beneficiary has not been previously tested using the same next-generation sequencing test, unless a new primary cancer diagnosis is made by the treating physician, and if the patient has decided to seek further cancer treatment. The test must have a U.S. Food and Drug Administration approved or cleared indication as an in vitro diagnostic, with results and treatment options provided to the treating physician for patient management.[152,]

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 16.

Table 16. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03576937	Achieving Value in Cancer Diagnostics: Blood Versus Tissue Molecular Profiling - a Prospective Canadian Study (VALUE)	207	Sep 2022
NCT01306045	Pilot Trial of Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies	471	Dec 2024
NCT03225664	BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer	37 (actual)	Sep 2024
NCT02622581	Clinical Research Platform into Molecular Testing, Treatment and Outcome of Non-Small Cell Lung Carcinoma Patients (CRISP)	12400	Dec 2027
NCT02117167[a]	Intergroup Trial UNICANCER UC 0105-1305/ IFCT 1301: SAFIR02_Lung - Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Non-small Cell Lung Cancer	999	Dec 2023
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Dec 2025

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02576431[a]	A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects With NTRK Fusion-positive Tumors	204	Aug 2025
NCT02568267[a]	An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements	700	Apr 2025
NCT01639508	A Phase II Study of Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity	86	Jul 2023
NCT03469960	A Randomized Phase 3 Trial Comparing Continuation Nivolumab-Ipilimumab Doublet Immunotherapy Until Progression Versus Observation in Treatment-naive Patients With PDL1-positive Stage IVNon-Small Cell Lung Cancer (NSCLC) After Nivolumab-Ipilimumab Induction Treatment	265	May 2023
NCT03199651	Beating Lung Cancer in Ohio (BLCIO) Protocol	2994	Dec 2023
NCT04863924	Accelerating Lung Cancer Diagnosis Through Liquid Biopsy (ACCELERATE)	170	Dec 2023
NCT04912687[a]	Implementing Circulating Tumor DNA Analysis at Initial Diagnosis to Improve Management of Advanced Non-small Cell Lung Cancer Patients (NSCLC) (CIRCULAR)	580	Jan 2024
NCT03037385[a]	A Phase 1/2 Study of the Highly-selective RET Inhibitor, BLU-667, in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors	589	Feb 2024
NCT03178552[a]	A Phase II/III Multicenter Study Evaluating the Efficacy and Safety of Multiple Targeted Therapies as Treatments for Patients With Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) Harboring Actionable Somatic Mutations Detected in Blood (B-FAST: Blood-First Assay Screening Trial)	1000	Apr 2024
NCT04591431	The Rome Trial - From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	384	Aug 2024
NCT04180176[a]	A Multicenter, Low-Interventional Study to Evaluate the Feasibility of a Prospective Clinicogenomic Program (PCG)	1000	Mar 2025

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Diagnosis and cancer type and stage
  - Previous treatment plan(s) and response(s)
  - Current treatment plan
  - Clinical justification for analysis testing
  - Previous biopsies and any tissue limitations or contraindications to repeat biopsy

Post Service (in addition to the above, please include the following):

- Analysis testing results

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
	0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden ***(Code effective 7/1/2022)***
	81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis
	81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis
	81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis
	81194	NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis
	81235	EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
	81404	Molecular Pathology Procedure Level 5
	81405	Molecular Pathology Procedure Level 6
	81406	Molecular Pathology Procedure Level 7
	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81479	Unlisted molecular pathology procedure
	88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
	88365	In situ hybridization (e.g., FISH), per specimen; initial single probe stain procedure

Type	Code	Description
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
11/26/2014	BCBSA Medical Policy adoption
08/31/2015	Policy title change from Molecular Analysis for Targeted Therapy for Non-Small-Cell Lung Cancer Policy revision without position change
06/01/2016	Policy revision without position change
12/01/2016	Policy revision without position change
12/01/2017	Policy revision without position change
12/01/2018	Policy revision without position change
12/01/2019	Policy revision without position change
12/01/2020	Annual review. Policy statement updated
01/01/2021	Annual review. Policy statement, guidelines and literature updated. Policy title changed from Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer to current one. Coding update.
03/01/2022	Annual review. No change to policy statement.
04/01/2022	Policy statement, guidelines and literature review updated to combine with Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy) 2.04.143. Policy title changed from Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer to current one.
09/01/2022	Coding update
02/01/2023	Annual review. Policy statement, guidelines and literature review updated. . Policy title changed from Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer to current one.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	AFTER Blue font: Verbiage Changes/Additions
Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer 2.04.45 **Policy Statement:** **Note:** Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review). The use of tissue samples for analysis is generally preferred over plasma testing (liquid biopsy or circulating tumor DNA, ctDNA) when available. Panel testing of tissue samples is an acceptable alternative to individual testing when the quantity of tissue is limited. Molecular analysis (genetic testing) is reserved for advanced (stage III or IV) or metastatic Non-Small-Cell Lung Cancer (NSCLC) including adenocarcinoma, large cell, squamous cell and NSCLC not otherwise specified (see Policy Guidelines) or if a targeted therapy dependent on genetic testing is being considered. Small panel testing including the following medically necessary genes may be considered as an alternative to individual testing and may be preferred when there is limited tissue available for testing.	Somatic (Tumor) Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB) 2.04.45 **Policy Statement:** **Note:** Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review). The use of tissue samples for analysis is generally preferred over plasma testing (liquid biopsy or circulating tumor DNA, ctDNA) when available. Panel testing of tissue samples is an acceptable alternative to individual testing when the quantity of tissue is limited. Plasma testing is generally unavailable for single genes or exons and are typically performed as a panel test. Molecular analysis related to this policy (genetic testing) is reserved for advanced (stage III or IV) or metastatic Non-Small-Cell Lung Cancer (NSCLC) including adenocarcinoma, large cell, squamous cell and NSCLC not otherwise specified (see Policy Guidelines) or if a targeted therapy dependent on genetic testing is being considered. Small panel tissue testing including the following medically necessary genes may be considered as an alternative to individual testing and may be preferred when there is limited tissue available for testing.

POLICY STATEMENT	
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I. Plasma tests for oncogenic driver variants deemed medically necessary on tissue biopsy may be considered **medically necessary** to predict treatment response to targeted therapy for patients meeting the following criteria: A. Patient does not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; AND B. Follow-up tissue-based analysis is planned when possible should no driver variant be identified via plasma testing.	***Plasma Testing When Tissue is Insufficient*** I. Plasma tests for oncogenic driver variants deemed medically necessary on tissue biopsy may be considered **medically necessary** to predict treatment response to targeted therapy for individuals when they do not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue. II. Follow-up tissue-based analysis may be considered **medically necessary** should no driver variant be identified via plasma testing.
***EGFR* Testing** II. Analysis of somatic variants (in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor *(EGFR)* gene, may be considered **medically necessary** to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], gefitinib [Iressa®], afatinib [Gilotrif®], or osimertinib [Tagrisso™]) in patients with advanced or high risk earlier stage (IB-IIIA) lung adenocarcinoma, large cell carcinoma, advanced squamous-cell non-small-cell lung cancer (NSCLC), and NSCLC not otherwise specified.	***EGFR* Testing** III. The epidermal growth factor receptor *(EGFR)* gene, may be considered **medically necessary** initially to predict treatment response to an FDA-approved therapy (e.g., erlotinib [Tarceva®] alone or in combination with ramucirumab [Cyramza®], gefitinib [Iressa®], afatinib [Gilotrif®], dacomitinib [Vizimpro®], or osimertinib [Tagrisso™]). Technically, the analysis of tumor tissue for somatic variants would be in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q). IV. Analysis of tumor tissue for somatic variants in exon 20 (e.g., insertion mutations) within the *EGFR* gene, may be considered **medically necessary** to predict treatment response to an FDA-approved therapy (e.g., mobocertinib [Exkivity] or amivantamab [Rybrevant]). However, testing is typically just ordered for EGFR analysis (alone or in a panel) rather than for specific exons.
III. At progression (or when included in an initial panel), analysis of the EGFR T790M resistance variant for targeted therapy with osimertinib using tissue or ctDNA may be considered **medically necessary** in patients with advanced or high risk earlier stage (IB-IIIA) lung adenocarcinoma, large cell carcinoma, advanced squamous-cell non-small-cell lung cancer, and non-small-cell lung cancer not otherwise specified.	V. At progression (or when included in an initial panel), repeat analysis of either a new tissue sample or plasma of (the EGFR T790M resistance variant) for targeted therapy with osimertinib may be considered **medically necessary** in individuals with advanced or high risk earlier stage (IB-IIIA) lung adenocarcinoma, large cell carcinoma, advanced squamous-cell non-small-cell lung cancer, and non-small-cell lung cancer not otherwise specified.

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	Patients with wild-type variants are unlikely to respond to targeted therapy; for these patients, other treatments should be considered.
IV. Analysis of other *EGFR* variants within exons 22 to 24, or other applications related to NSCLC, is considered **investigational**.	VI. Analysis of somatic variants in the EGFR gene in tissue or plasma, including variants within exons 22 to 24, is considered **investigational** in all other situations unless included in the general analysis of EGFR.
***ALK* Testing**	
V. Analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (*ALK*) gene may be considered **medically necessary** to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], or brigatinib [Alunbrig™]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section) or when included in a panel approved for other indications.	***ALK* Testing** VII. Individual analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (*ALK*) gene may be considered **medically necessary** to predict treatment response to an FDA-approved ALK inhibitor therapy (e.g., crizotinib [Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], brigatinib [Alunbrig™], or lorlatinib [Lorbrena®]) or when part of an approved panel.
VI. Analysis of somatic rearrangement variants of the *ALK* gene is considered **investigational** in all other situations.	VIII. Analysis of somatic rearrangement variants of the *ALK* gene in tissue or plasma is considered **investigational** in all other situations.
***BRAF* V600E Testing**	
VII. Analysis of the somatic *BRAF* V600E variant may be considered **medically necessary** to predict treatment response to BRAF or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]), in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section) or when included in a panel approved for other indications.	***BRAF* V600E Testing** IX. Individual analysis of the somatic *BRAF* V600E variant may be considered **medically necessary** to predict treatment response to an FDA-approved BRAF and/or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]), or when part of an approved panel.
VIII. Analysis of the somatic *BRAF V600E* variant is considered **investigational** in all other situations.	X. Analysis of tumor tissue for the somatic *BRAF* V600E variant is considered **investigational** in all other situations.

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***ROS1* Testing** IX. Analysis of somatic rearrangement variants of the *ROS1* gene may be considered **medically necessary** to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section) or when included in a panel approved for other indications. X. Analysis of somatic rearrangement variants of the *ROS1* gene is considered **investigational** in all other situations.	***ROS1* Testing** XI. Individual analysis for somatic rearrangement variants of the *ROS1* gene may be considered **medically necessary** to predict treatment response to an FDA-approved ROS1 inhibitor therapy (e.g., crizotinib [Xalkori®] or entrectinib [Rozlytrek®]) or when part of an approved panel. XII. Analysis of somatic rearrangement variants of the *ROS1* gene is considered **investigational** in all other situations.
***KRAS* Testing** XI. Analysis of somatic variants of the *KRAS* gene may be considered **medically necessary** to predict treatment response to sotorasib (Lumakras) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section) or when included in a panel approved for other indications. XII. All other uses of analysis of somatic variants of the *KRAS* gene are considered **investigational**.	***KRAS* Testing** XIII. Individual analysis of somatic variants of the *KRAS* gene (e.g., G12C) may be considered **medically necessary** to predict treatment response to sotorasib (Lumakras) or when part of an approved panel. XIV. All other uses of analysis of somatic variants of the *KRAS* gene are considered **investigational**.
***HER2* Testing** XIII. Analysis of somatic alterations in the *HER2* gene in tissue for targeted therapy in patients with NSCLC is considered **investigational** unless included in a panel approved for other indications.	***HER2* Testing** XV. Individual analysis of somatic alterations in the *HER2* (*ERBB2*) gene may be considered **medically necessary** to predict treatment response to an FDA-approved therapy (e.g., fam-trastuzumab deruxtecan-nxki [Enhertu®]) or when part of an approved panel.
***NTRK* Gene Fusion Testing** XIV. Analysis of somatic *NTRK* gene fusions in tissue may be considered **medically necessary** to predict treatment response to entrectinib (Rozlytrek) or larotrectinib (Vitrakvi) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section) or when included in a panel approved for other indications.	XVI. All other uses of analysis of somatic variants of the *HER2* (*ERBB2*) gene are considered **investigational**.

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XV. Analysis of somatic *NTRK* gene fusions is considered **investigational** in all other situations.	
***RET* Rearrangement Testing**	***RET* Rearrangement Testing**
XVI. Analysis of somatic alteration in the *RET* gene may be considered **medically necessary** to predict treatment response to pralsetinib (Gavreto) or selpercatinib (Retevmo) in patients with metastatic NSCLC or when included in a panel approved for other indications.	XVII. Individual analysis of somatic alterations in the *RET* gene may be considered **medically necessary** to predict treatment response to pralsetinib (Gavreto) or selpercatinib (Retevmo) or when part of an approved panel.
XVII. Analysis of somatic alterations in the RET gene is considered **investigational** in all other situations.	XVIII. Analysis of tumor tissue for somatic alterations in the *RET* gene is considered **investigational** in all other situations.
***MET* Exon 14 Skipping Alteration**	***MET* Exon 14 Skipping Alteration**
XVIII. Analysis of somatic alteration in tissue that leads to *MET* exon 14 skipping may be considered **medically necessary** to predict treatment response to capmatinib (Tabrecta) in patients with metastatic NSCLC.	XIX. Individual analysis of somatic alterations that leads to *MET* exon 14 skipping may be considered **medically necessary** to predict treatment response to capmatinib (Tabrecta) or when part of an approved panel.
XIX. Analysis of genetic alterations of the *MET* gene is considered **investigational** in all other situations.	XX. All other uses of analysis of somatic variants of the *MET* gene in tissue or plasma are considered **investigational**.
PD-L1 Testing	**PD-L1 Testing**
XX. Programmed Death-Ligand 1 (PD-L1) testing may be considered **medically necessary** to predict treatment response to atezolizumab (Tecentriq), nivolumab (Opdivo) in combination with ipilimumab (Yervoy), or pembrolizumab (Keytruda) in patients with metastatic NSCLC. **Note:** PD-L1 is a ligand not a gene, and testing may be requested separately if not part of the panel.	XXI. Programmed Death-Ligand 1 (PD-L1) testing may be considered **medically necessary** to predict treatment response to an FDA-approved therapy (e.g., atezolizumab [Tecentriq], nivolumab [Opdivo] in combination with ipilimumab [Yervoy], pembrolizumab [Keytruda], or cemiplimab-rwlc [Libtayo]) in individuals with NSCLC or when part of an approved panel. **Note:** PD-L1 is a ligand not a gene, and testing may be requested separately if not part of the panel.
XXI. PD-L1 testing is considered **investigational** in all other situations.	XXII. PD-L1 testing is considered **investigational** in all other situations.

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Tumor Mutational Burden Testing XXII. Analysis of tumor mutational burden for targeted therapy in patients with NSCLC is considered **investigational**.	Tumor Mutational Burden Testing XXIII. Analysis of tumor mutational burden to predict treatment response to immunotherapy (e.g., pembrolizumab or Keytruda) in individuals with resistant or progressive cancer that has failed all standard regimens may be considered **medically necessary**. XXIV. Analysis of tumor mutational burden is considered **investigational** in all other circumstances.